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Ursodiol (Ursodeoxycholic Acid)

Updated: September 25, 2017.

OVERVIEW

Introduction

Ursodeoxycholic acid or ursodiol is a naturally occurring bile acid that is used dissolve cholesterol gall stones and to treat cholestatic forms of liver diseases including primary biliary cirrhosis. Ursodiol has been linked to rare instances of transient and mild serum aminotransferase elevations during therapy and to rare instances of jaundice and worsening of liver disease in patients with preexisting cirrhosis.

Background

Ursodiol (ur" soe dye' ol) is a naturally occurring bile acid that is a minor fraction of the bile acid pool in humans, but a major fraction in bears and other hibernating animals. Ursodeoxycholic acid is more water soluble (hydrophilic) than cholic or chenodeoxycholic acid and is less inherently toxic to cells. When given orally, ursodeoxycholic acid becomes a major component of the bile acid pool, the proportion rising from <2% to as much as 65%. By replacing the hydrophobic or more toxic bile acids with ursodiol, the toxic effects of cholestasis are ameliorated. Unlike other primary bile acids, ursodiol has little agonist activity with FXR, the bile acid sensing nuclear receptor. As a consequence, ursodiol has little effect on cholesterol and lipid synthesis and is effective in reducing the cholesterol saturation of bile and in dissolving cholesterol gallstones. In addition, ursodiol has been shown to decrease serum enzyme elevations in a large number of cholestatic liver diseases including primary biliary cirrhosis, the cholestasis of pregnancy, and parenteral nutrition associated liver disease. In some situations, this improvement in liver enzyme levels has been accompanied by improvements in symptoms, liver histology and long term adverse outcomes of these diseases (cirrhosis, end stage liver disease). Ursodiol was approved for dissolution of gallstones in 1987 and as a therapy of primary biliary cirrhosis in 1996. It is also used off label in other cholestatic liver conditions including sclerosing cholangitis, graft-vs-host disease, cholestasis of pregnancy and the liver disease of cystic fibrosis. Ursodiol is available in tablets and capsules of 250 and 300 mg generically and under brand names such as Actigall and Urso. The typical initial dose for dissolution of gall stones is 8 to 10 mg/kg daily and for primary biliary cirrhosis is 13 to 15 mg daily in three divided doses with meals. Ursodiol is generally well tolerated; uncommon side effects can include fatigue, nausea, headache and weight gain. Less common, but potentially severe adverse reactions include hypersensitivity reactions and depression.

Hepatotoxicity

n multiple clinical trials in a variety of conditions, ursodiol has not been found to cause increases in serum enzyme elevations, worsening of underlying liver disease or clinically apparent liver injury. Nevertheless, there have been rare reports of clinical decompensation in patients with advanced liver disease and cirrhosis started

on ursodiol, but the reason for such reactions is not known. In at least one instance, there was recurrence of jaundice on restarting ursodiol. Thus, ursodiol has beneficial effects on several forms of liver disease and has not been convincingly linked to cases of clinically apparent acute liver injury in patients without cirrhosis. There is some concern that ursodiol may be harmful in patients with advanced liver disease (Childs class B and C) and such patients probably should not receive ursodiol.

Likelihood score: D (possible rare cause of acute decompensation of preexisting liver disease).

Mechanism of Liver Injury

The mechanism by which ursodiol might cause liver injury is unclear as it is a natural occurring bile acid that is concentrated in the liver and usually replaces and suppresses the synthesis of more hydrophobic and potentially toxic bile acids. The rare instancers of worsening of liver disease during ursodiol therpay may be caused by the choleresis (increase in bile flow) that it stimulates rather to any intrinsic or idiosyncratic reaction to the drug itself.

Outcome and Management

Patients with cirrhosis who are started on ursodiol should be monitored regularly for the first few months, and treatment discontinued if there is evidence of worsening of liver tests or of hepatic decompensation. There does not appear to be cross sensitivity to liver injury or adverse events between ursodiol and other bile acid therapies.

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

Drug Class: Gastrointestinal Agents, Bile Acids

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ursodiol – Generic, Actigall®

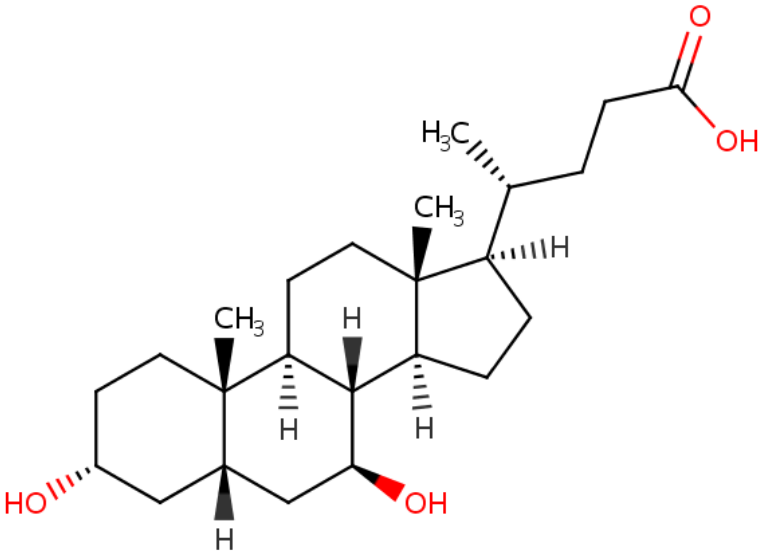
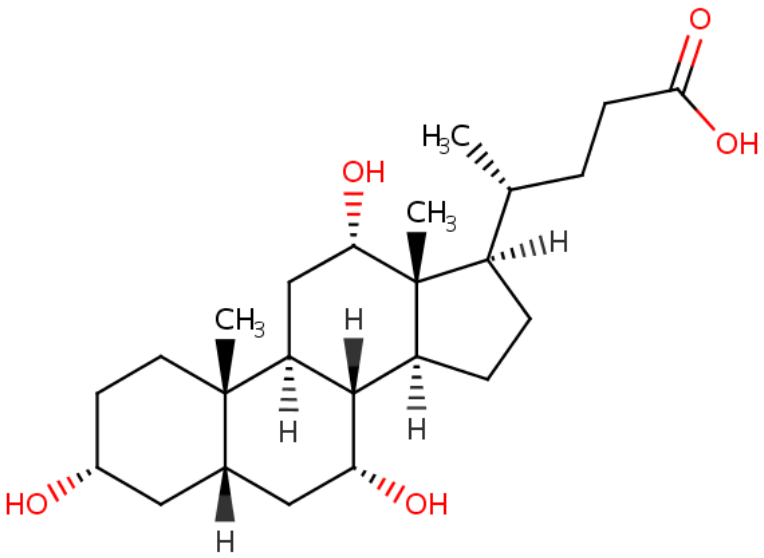
DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ursodiol	128-13-2	C24-H40-O4	
Cholic Acid	81-25-4	C24-H40-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 25 September 2017

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

Zimmerman HJ. Bile acid derivatives. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 721.

(Review of hepatotoxicity published in 1999; mentions that ursodiol is an isomer of chenodiol and poses "little demonstrable risk of hepatic injury" in humans, although it causes liver injury in rabbits and rhesus monkeys).

Sharkey KA, Wallace JL. Treatment of disorders of bowel motility and water flux: anti-emetics; agents used in biliary and pancreatic disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1323-50.

(Textbook of pharmacology and therapeutics).

Schoenfield LJ, Lachin JM. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Study. A controlled trial of efficacy and safety. Ann Intern Med 1981; 95; 257-82. PubMed PMID: 7023307.

(Among 916 patients with radiolucent gallstones treated with chenodiol [350 or 750 mg daily] vs placebo for 2 years, gallstone dissolution occurred in 5% and 13.5% vs 0% and ALT elevations in 13-19% vs 13%, which were above 3 times ULN in 5-8% vs 4% while biopsies showed nonspecific changes only; ALT elevations resolved even without stopping in most and among 17 who stopped therapy, 6 had recurrence on restarting; no patient developed clinically apparent liver injury).

Miyai K, Javitt NB, Gochman N, Jones HM, Baker D. Hepatotoxicity of bile acids in rabbits: ursodeoxycholic acid is less toxic than chenodeoxycholic acid. Lab Invest 1982; 46: 428-37. PubMed PMID: 7200166.

(Feeding rabbits chenodeoxycholic and lithocholic acid led to increases in ALT levels, histologic changes in the liver and significant mortality compared to no treatment or use of ursodiol).

Roda E, Bazzoli F, Labate AM, Mazzella G, Roda A, Sama C, Festi D, et al. Ursodeoxycholic acid vs. chenodeoxycholic acid as cholesterol gallstone-dissolving agents: a comparative randomized study. Hepatology 1982; 2: 804-10. PubMed PMID: 7141392.

(Among 223 patients with gallstones treated with ursodiol or chenodiol at 2 doses for 12 months, gallstone dissolution was similar at the higher doses but greater for ursodiol at the lower doses; ALT elevations occurred only in chenodiol groups [14%], but there were no concurrent elevations in Alk P or bilirubin).

Fromm H, Roat JW, Gonzalez V, Sarva RP, Farivar S. Comparative efficacy and side effects of ursodeoxycholic and chenodeoxycholic acids in dissolving gallstones. A double-blind controlled study. Gastroenterology 1983; 85: 1257-64. PubMed PMID: 6354826.

(Among 60 patients with radiolucent gallstones treated with chenodiol [375 or 750 mg] or ursodiol [400 or 800 mg] or placebo daily, complete dissolution occurred in 7% on chenodiol versus 30% on ursodiol, but none on placebo, while ALT elevations above 3 times ULN occurred in 2 of 26 on chenodiol but none of 24 on ursodiol).

Erlinger S, Le Go A, Husson JM, Fevery J. Franco-Belgian cooperative study of ursodeoxycholic acid in the medical dissolution of gallstones: a double-blind, randomized, dose-response study, and comparison with chenodeoxycholic acid. Hepatology 1984; 4: 308-14. PubMed PMID: 6706305.

(Among 197 patients with radiolucent gallstones treated with ursodiol or chenodiol, stone dissolution rates were similar, but diarrhea was less with ursodiol [5% vs 23%] and ALT elevations were transient and mild [less than twice normal] in all except one patient [3%] on chenodiol).

Fisher MM, Roberts EA, Rosen IE, Shapero TF, Sutherland LR, Davies RS, Bacchus R, Lee SV. The Sunnybrook Gallstone Study: a double-blind controlled trial of chenodeoxycholic acid for gallstone dissolution. Hepatology 1985; 5: 102-7. PubMed PMID: 3881327.

(Among 160 patients with radiolucent gallstones treated with chenodiol [375 or 750 mg daily] or placebo for 2 years, stone dissolution occurred in 11-13% vs 0% and no patient developed clinically apparent liver injury).

Nakashima T, Sano A, Seto Y, Nakajima T, Okuno T, Takino T. A case of hyperbilirubinemia during treatment with chenodeoxycholic acid. Jpn J Med 1987; 26: 404-8. PubMed PMID: 3694926.

(A 27 year old woman with acute, symptomatic cholelithiasis developed jaundice within 6 weeks of starting chenodiol [peak values 12.8 mg/dL, ALT normal, Alk P ~3 times ULN], resolving upon stopping, but later requiring cholecystectomy).

Vogel W, Kathrein H, Judmaier G, Braunsteiner H. Deterioration of primary biliary cirrhosis during treatment with ursodeoxycholic acid. Lancet 1988; 1 (8595): 1163. PubMed PMID: 2896978.

(64 year old man with PBC and early cirrhosis developed jaundice and ascites 2 months after starting ursodiol [bilirubin "tripled", ALT and Alk P levels "almost doubled"], with resolution on stopping, but recurrence of jaundice [bilirubin 8 mg/dL] and decompensation within days of restarting).

Poupon R, Poupon RE. Deterioration in primary biliary cirrhosis in patient on ursodeoxycholic acid. Lancet 1988; 2 (8603): 166-7. Reply by Authors. PubMed PMID: 2899219.

(Letter in response to Vogel et al [1988] suggesting that the hepatic decompensation was due to portal vein thrombosis or arterio-portal fistula from a liver biopsy rather than ursodiol; reply by the authors stating that the patient had not had a liver biopsy for 17 years and had no evidence of thrombosis or fistula on imaging).

Fisher RL, Hofmann AF, Converse JL, Rossi SS, Lan SP. The lack of relationship between hepatotoxicity and lithocholic-acid sulfation in biliary bile acids during chenodiol therapy in the National Cooperative Gallstone Study. Hepatology 1991; 14: 454-63. PubMed PMID: 1874490.

(Testing of bile samples from 31 patients with gallstones treated with chenodiol with and without liver test or liver biopsy abnormalities showed no differences in lithocholate levels during treatment with or without liver test abnormalities).

Poupon RE, Balkau B, Eschwège E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. UDCA-PBC Study Group. N Engl J Med 1991; 324: 1548-54. PubMed PMID: 1674105.

(Among 146 patients with PBC treated with ursodiol [13-15 mg daily] or placebo for 2 years, ALT, Alk P and bilirubin levels and liver histology [except for fibrosis] improved with ursodiol but not placebo; one patient on ursodiol required discontinuation because of worsening of pruritus; no mention of hepatotoxicity or other toxicities).

Beuers U, Spengler U, Kruis W, Aydemir U, Wiebecke B, Heldwein W, Weinzierl M, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. Hepatology 1992; 16: 707-14. PubMed PMID: 1505913.

(Among 14 patients with sclerosing cholangitis treated with ursodiol [13-15 mg/kg daily] or placebo for 1 year, Alk P, ALT and bilirubin improved with ursodiol and only one patient stopped ursodiol early because of side effects [diarrhea]).

Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez MC, Hernandez I, Alvarez C, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology 1992; 15: 1043-7. PubMed PMID: 1592342.

(Among 8 patients with intrahepatic cholestasis of pregnancy treated with ursodiol [1 gm daily], all had marked improvements in Alk P, ALT and bilirubin levels and pruritus scores, all relapsing upon stopping therapy and responding again on restarting; no evidence of hepatotoxicity or significant toxicity).

Dubner H, Fromm H. Ursodeoxycholic acid treatment of intrahepatic cholestasis of pregnancy: observations on efficacy and safety. Gastroenterology 1993; 104: 660-1. PubMed PMID: 8425713.

(Commentary on Palma [1992] discussing the natural history of intrahepatic cholestasis of pregnancy and the need to better demonstrate the safety of ursodiol in pregnancy).

Daugherty CC, Setchell KD, Heubi JE, Balistreri WF. Resolution of liver biopsy alterations in three siblings with bile acid treatment of an inborn error of bile acid metabolism(delta 4-3-oxosteroid 5 beta-reductase deficiency). Hepatology 1993; 18: 1096-101. PubMed PMID: 8225213.

(Among 3 siblings with a bile acid synthetic defect and severe liver disease, treatment with cholic acid and ursodiol was followed by resolution of jaundice and improvements in ALT, Alk P and liver histology).

Heathcote EJ, Cauch-Dudek K, Walker V, Bailey RJ, Blendis LM, Ghent CN, Michieletti P, et al. The Canadian Multicenter Double-blind Randomized Controlled Trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994; 19: 1149-56. PubMed PMID: 8175136.

(Among 222 patients with PBC treated with ursodiol [14 mg/kg daily] or placebo for 24 months, ALT, Alk P and bilirubin levels and some features of histology [not fibrosis] improved with ursodiol therapy, but symptoms did not change and there were no differences in rates of death or liver transplantation; no mention of hepatotoxicity).

Lindor KD, Dickson ER, Baldus WP, Jorgensen RA, Ludwig J, Murtaugh PA, Harrison JM, et al. Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterology 1994; 106: 1284-90. PubMed PMID: 8174890.

(Among 180 patients with PBC treated with ursodiol [13-15 mg/kg daily] or placebo for up to 4 years, there were improvements in Alk P, ALT, AST and bilirubin with ursodiol, but no significant change in liver histology or symptoms and a nonsignificant decrease in liver transplantation and mortality; no mention of ALT elevations or hepatotoxicity).

Combes B, Carithers RL Jr, Maddrey WC, Lin D, McDonald MF, Wheeler DE, Eigenbrodt EH, et al. A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995; 22: 759-66. PubMed PMID: 7657280.

(Among 151 patients with PBC treated with ursodiol [10-12 mg/kg] or placebo for 2 years, decreases in bilirubin, ALT and Alk P as well as histological features improved mostly in patients with earlier stage disease, but there was no overall effect on rates of mortality or liver transplantation).

Bashir RM, Lewis JH. Hepatotoxicity of drugs used in the treatment of gastrointestinal disorders. Gastroenterol Clin North Am 1995; 24: 937-67. PubMed PMID: 8749906.

(Review of hepatotoxicity of drugs for gastrointestinal disease mentions that ALT elevations occur in up to 30% of patients treated with chenodiol and are above 3-4 times ULN in 2-3%, and that there have been at least 4 cases of clinically apparent liver injury reported to the sponsor whereas no such reports have been linked to ursodiol; no specific details of cases given).

Colombo C, Battezzati PM, Podda M, Bettinardi N, Giunta A. Ursodeoxycholic acid for liver disease associated with cystic fibrosis: a double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis. Hepatology 1996; 23: 1484-90. PubMed PMID: 8675168.

(Among 55 patients with cystic fibrosis with liver disease treated with ursodiol [15 mg/kg daily], taurine, both or placebo, GGT, ALT and AST levels improved more in ursodiol treated patients and "no severe side effects were reported", although one ursodiol treated patient developed jaundice and decompensation after 7 months and was withdrawn and underwent liver transplantation).

Hempfling W, Dilger K, Beuers U. Systematic review: ursodeoxycholic acid--adverse effects and drug interactions. Aliment Pharmacol Ther 2003; 18: 963-72. PubMed PMID: 14616161.

(Systematic review of side effects of ursodiol mentions that no severe adverse events or liver toxicities were reported in controlled clinical trials for gallstones or chronic cholestatic liver diseases, but instances of clinical decompensation were reported in patients with preexisting cirrhosis, suggesting that it should be used with caution in patients with advanced disease).

Combes B, Emerson SS, Flye NL, Munoz SJ, Luketic VA, Mayo MJ, McCashland TM, et al. Methotrexate (MTX) plus ursodeoxycholic acid (UDCA) in the treatment of primary biliary cirrhosis. Hepatology 2005; 42: 1184-93. PubMed PMID: 16250039.

(Among 265 patients with PBC treated with ursodiol with or without methotrexate for a median of 7.6 years, transplant-free survival was excellent and not affected by methotrexate therapy; no mention of unexplained ALT elevations or hepatotoxicity).

Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol 2006; 3: 318-28. PubMed PMID: 16741551.

(Review of the mechanism of action of ursodiol in cholestatic liver diseases).

Paumgartner G. Medical treatment of cholestatic liver diseases: From pathobiology to pharmacological targets. World J Gastroenterol 2006; 12: 4445-51. PubMed PMID: 16874853.

(Review of the pathogenesis of gallstone formation and medical therapies for gallstone dissolution).

Chiang JY. Bile acids: regulation of synthesis. J Lipid Res 2009; 50: 1955-66. PubMed PMID: 19346330.

(Review of the pathways of cholic and chenodeoxycholic acid synthesis and their regulation via FXR, FGF19, FGFR4 and CYP7A1).

Gonzales E, Gerhardt MF, Fabre M, Setchell KD, Davit-Spraul A, Vincent I, Heubi JE, et al. Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. Gastroenterology 2009; 137: 1310-1320. PubMed PMID: 19622360.

(Among 15 patients with bile acid synthesis defects treated with oral bile acids [ursodiol and cholic acid initially and eventually cholic acid alone for all except one patient: 3-9 mg/kg daily] for 5-15 years, all had lasting clinical improvements shown by repeat liver biopsies in 14; overdose of cholic acid was marked by diarrhea, pruritus and increases in GGT and ALT that responded to dose modification).

Braga MF, Grace MG, Lenis J, Kennedy FP, Teplinsky AL, Roederer G, Palumbo PJ, et al. Efficacy and safety of ursodeoxycholic acid in primary, type IIa or IIb hypercholesterolemia: a multicenter, randomized, double-blind clinical trial. Atherosclerosis 2009; 203: 479-82. PubMed PMID: 18801487.

(Among 125 patients with hypercholesterolemia treated with ursodiol [13-15 mg/kg daily] or placebo for 24 weeks, changes in total, LDL and HDL cholesterol levels were similar in the two groups, while digestive disease complaints and withdrawals for adverse events were more common with ursodiol; no mention of ALT elevations or hepatotoxicity).

Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009; 50: 808-14. PubMed PMID: 19585548.

(Among 150 patients with primary sclerosing cholangitis treated with ursodiol [high doses: 28-30 mg/kg daily] or placebo for up to 5 years, improvements in ALT, Alk P and bilirubin were more common with ursodiol, but so were serious adverse events and clinical outcomes [death, liver transplantation and complications of cirrhosis]).

Imam MH, Sinakos E, Gossard AA, Kowdley KV, Luketic VA, Edwyn Harrison M, McCashland T, et al. High-dose ursodeoxycholic acid increases risk of adverse outcomes in patients with early stage primary sclerosing cholangitis. Aliment Pharmacol Ther 2011; 34: 1185-92. PubMed PMID: 21957881.

(Secondary analysis of trial of high dose ursodiol vs placebo in primary sclerosing cholangitis [Lindor 2009] found that the excess in mortality and complications of cirrhosis occurred in patients with earlier stage disease [endpoints occurring in 15.9% vs 4.5% with early stage disease]).

Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, Sogni P, et al.; FRESGUN. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol 2011; 54: 1011-9. PubMed PMID: 21145828.

(Among 126 patients with nonalcoholic steatohepatitis treated with ursodiol vs placebo for 12 months, serum ALT and GGT improved more with ursodiol and no patient in either group developed cirrhosis or died of liver disease; no mention of marked ALT elevations or hepatotoxicity).

Eaton JE, Silveira MG, Pardi DS, Sinakos E, Kowdley KV, Luketic VA, Harrison ME, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011; 106: 1638-45. PubMed PMID: 21556038.

(Among 56 patients with sclerosing cholangitis and ulcerative colitis treated with high dose ursodiol or placebo for up to 5 years [Lindor 2009], those receiving ursodiol had a higher rate of colorectal cancer, the difference arising after 2.5 years of therapy).

Song P, Zhang Y, Klaassen CD. Dose-response of five bile acids on serum and liver bile acid concentrations and hepatotoxicty in mice. Toxicol Sci 2011; 123: 359-67. PubMed PMID: 21747115.

(Feeding of various concentrations of 5 different bile acids to mice demonstrated clear toxicity with lithocholic, cholic, deoxycholic and chenodeoxycholic acid, but little or no toxicity with ursodeoxycholic acid).

Joutsiniemi T, Timonen S, Leino R, Palo P, Ekblad U. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: a randomized controlled trial. Arch Gynecol Obstet 2014; 289: 541-7. PubMed PMID: 23978872.

(Among 20 pregnant women with intrahepatic cholestasis of pregnancy treated with ursodiol [450 mg daily] or placebo for 14 days, itching scores and serum levels of ALT and bilirubin improved more with ursodiol than placebo treatment).

Xue Q, Peng T, Wang J. [Ursodeoxycholic acid-induced hepatic disease: a case report]. Zhonghua Gan Zang Bing Za Zhi 2015; 23: 714-5. Chinese. PubMed PMID: 26524371.

(49 year old woman with suspected autoimmune hepatitis developed jaundice within a few days of starting ursodiol [bilirubin 9.1 mg/dL, ALT 724 U/L, Alk P 255 U/L] which improved on stopping and recurred upon restarting ursodiol at a lower dose).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to ursodiol or other bile acid therapies).

Parízek A, Simják P, Cerný A, Sestinová A, Zdenková A, Hill M, Dusková M, et al. Efficacy and safety of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Ann Hepatol 2016; 15: 757-61. PubMed PMID: 27493115.

(Among 191 pregnant women with intrahepatic cholestasis of pregnancy treated with ursodiol, liver test abnormalities improved in 86% and therapy was well tolerated with minor side effects only, including diarrhea [5%] and skin rash [0.5%]; no mention of ALT elevations or worsening of liver disease).

Assis DN, Abdelghany O, Cai SY, Gossard AA, Eaton JE, Keach JC, Deng Y, et al. Combination therapy of all-trans retinoic acid with ursodeoxycholic acid in patients with primary sclerosing cholangitis: a human pilot study. J Clin Gastroenterol 2017; 51: e11-e16. PubMed PMID: 27428727.

(Among 19 patients treated with ursodiol to which was added all-trans retinoic acid, 4 withdrew early and in the remaining 15 there was a slight decrease in serum Alk P [277 to 243 U/L] and ALT levels [76 to 46 U/L], which rose to pretreatment levels upon stopping the retinoic acid).

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 [5-10 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%]).