Ursodeoxycholic Acid Therapy in Hepatobiliary Disease

Kris V. Kowdley, MD

Ursodeoxycholic acid is a hydrophilic bile acid that under normal circumstances represents a small fraction of the bile acid pool in humans. It is effective in dissolving cholesterol gallstones in appropriately selected patients. Ursodeoxycholic acid improves serum alkaline phosphatase and aminotransferase levels in primary biliary cirrhosis, but its effects on rates of liver transplantation and death are less certain. Ursodeoxycholic acid has no promising effects in several other cholestatic liver diseases, such as cystic fibrosis and intrahepatic cholestasis of pregnancy, but data are too preliminary to make recommendations about its routine use in these conditions. Its effects are mediated by amelioration of damage to cell membranes caused by retained toxic bile acids. Ursodeoxycholic acid improves biliary secretion of bile acids, may improve bile flow, and it has immunomodulatory properties that may reduce immune-mediated liver damage. However, its use in the treatment of cholestatic liver disease remains uncertain pending additional randomized trials. **Am J Med. 2000;108:481–486.** ©2000 by Excerpta Medica, Inc.

Bile acids, the major constituents of bile, are synthesized in the liver from cholesterol. Because of their unique biochemical characteristics, bile acids assist in the absorption and transport of dietary lipids and fat-soluble vitamins. They may be classified into primary bile acids, which are synthesized in the liver, and secondary bile acids, which are formed in the intestine by hydroxylation of primary bile acids by intestinal bacteria (1). The major primary bile acids include cholic acid and chenodeoxycholic acid. Deoxycholic acid and lithocholic acid comprise the secondary bile acids. Ursodeoxycholic acid, which is derived from chenodeoxycholic acid, represents a small fraction of the normal bile acid pool in humans (less than 5%).

Bile acids have both hydrophobic and hydrophilic properties that enable them to function as detergents. However, the different bile acids have variable degrees of hydrophobicity and hydrophilicity, which are determined by their biochemical and physiochemical properties. Lithocholic acid is the least water soluble, whereas ursodeoxycholic acid is much more hydrophilic. Cholic acid and chenodeoxycholic acid have intermediate degrees of hydrophilicity (2).

Liver disease can lead to decreased hepatic uptake, synthesis, and transport of bile acids. Most chronic cholestatic liver diseases result from progressive destruction or loss of intrahepatic or extrahepatic bile ducts. Diseases of the biliary tract or of the bile duct epithelium may also lead to failure in the transport of bile acids into bile ducts and, consequently, increased serum concentrations of bile acids. A common feature of these disorders is the accumulation of bile acids in the liver and blood, presumably because of decreased biliary secretion. Bile flow is also reduced in these patients.

Liver damage in chronic cholestasis is largely mediated by the effects of high concentrations of retained hydrophobic bile acids in the liver. Several studies have shown that hydrophobic bile acids, such as lithocholic acid and its precursor chenodeoxycholic acid, are hepatotoxic (3). These hydrophobic bile acids may solubilize membrane-bound lipids, leading to damage to cell membranes, disruption of cellular integrity, leakage of intracellular components, and hepatocellular necrosis (4). Cholestasis may also lead to liver damage by immune activation (5,6).

Liver damage in many chronic cholestatic liver diseases may be the result of a combination of immunologic bile duct injury and hepatotoxicity resulting from retained hydrophobic bile acids (5). Hepatocellular damage and fibrosis may ultimately lead to cirrhosis and liver failure.

THERAPY OF CHOLESTATIC LIVER DISEASES

Ursodeoxycholic acid can be used to treat many cholestatic liver diseases and holds promise for the treatment of several other noncholestatic liver diseases in which bile secretion may be impaired (Table). Ursodeoxycholic acid, a 7-β epimer of chenodeoxycholic acid, was first

From the Division of Gastroenterology/Hepatology, University of Washington, School of Medicine, Seattle, Washington.

Supported in part by an unrestricted grant from Axcan Pharma.

Requests for reprints should be addressed to 1959 NE Pacific Street, Box 356174, University of Washington, Seattle, Washington 98195.

Manuscript submitted March 30, 1999, and accepted in revised form December 7, 1999.

Table. Liver Diseases Treated with Ursodeoxycholic Acid

Primary biliary cirrhosis
Primary sclerosing cholangitis
Intrahepatic cholestasis of pregnancy
Graft-versus-host disease of the liver
Liver disease associated with cystic fibrosis
Cholestasis resulting from total parenteral nutrition
Hepatic allograft rejection
Nonalcoholic steatohepatitis
Veno-occlusive disease of the liver

identified in the dried bile of the Chinese black bear (7). It is efficiently taken up in the liver, conjugated primarily with glycine, and secreted into the bile with subsequent enterohepatic circulation. Administration of ursodeoxycholic acid in normal subjects results in increased bile flow and increased secretion of bile acids into bile (8). Biliary enrichment with ursodeoxycholic acid increases by up to 50%, and is accompanied by a decrease in chenodeoxycholic acid and cholic acid (9).

There are several proposed mechanisms for the favorable effects of ursodeoxycholic acid in cholestatic liver diseases (3) (Figure 1). These can be classified into three broad categories: hepatoprotective effects, effects on endogeneous bile acids and bile flow, and immunomodulation.

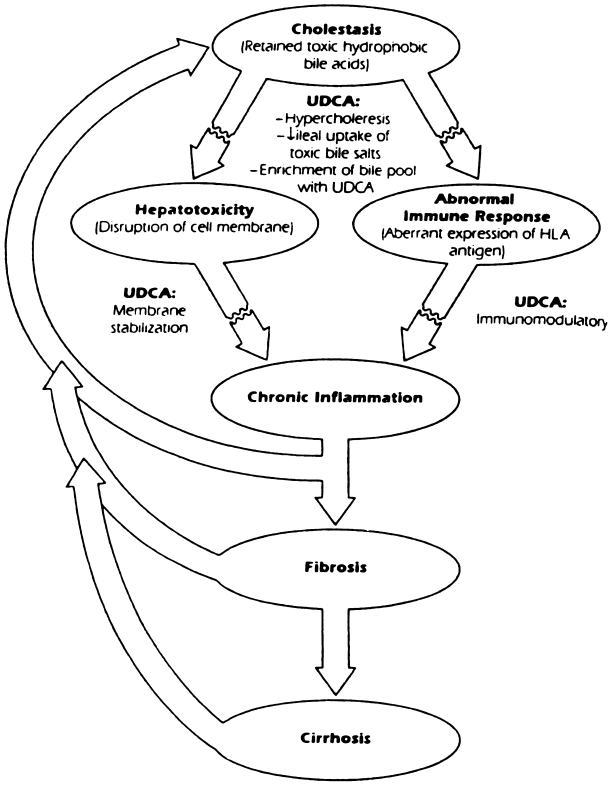

Figure 1. Mechanisms of action of ursodeoxycholic acid in chronic liver disease. Reprinted with permission from (13).

Hepatoprotective Effects

The hepatoprotective effects of ursodeoxycholic acid are largely related to its displacement of more hydrophobic and toxic bile acids that accumulate in the setting of cholestasis. One possible mechanism may be the inhibition of solubilization of membrane-bound cholesterol and phospholipids (10), which appears to be mediated by reconstitution of the bile acid pool with a greater proportion of ursodeoxycholic acid. As shown in Figure 2, after 6 months of treatment with ursodeoxycholic acid at doses of 10 to 12 mg/kg/day, ursodeoxycholic acid represents 40% to 50% of the bile acid pool (8).

Effect on Biliary Transport

Ursodeoxycholic acid has several potential benefits on biliary physiology. It results in choleresis, with increased capacity of bile duct cells to secrete hydrophobic bile acids and a reduction in serum levels of chenodeoxycholic acid in patients with primary biliary cirrhosis (3,4). Biliary secretion of phospholipids, which may also be hepatoprotective, appears to be increased with ursodeoxycholic acid therapy. The reduction in serum bilirubin levels with ursodeoxycholic acid therapy among patients with primary biliary cirrhosis and primary sclerosing cholangitis is probably related to enhanced biliary transport (11).

Immunomodulatory Effects

Aberrant expression of major histocompatability complex (MHC) class I antigens on hepatocytes has been described in rats with extrahepatic obstruction caused by bile duct ligation (12). Patients with cholestasis resulting from primary biliary cirrhosis also have aberrant expression of MHC class I antigens on hepatocytes and bile duct cells. Hepatocytes expressing these antigens could be a target for immune-mediated destruction by activated lymphocytes, leading to hepatocellular damage. Treatment with ursodeoxycholic acid reduces the expression of class I antigens on hepatocytes in several cholestatic liver diseases (6). Therefore, it seems plausible that ursodeoxycholic acid could reduce the antigenic stimulus for T cells that target hepatocytes with altered MHC class I antigen expression.

CLINICAL RESULTS WITH URSODEOXYCHOLIC ACID IN CHOLESTATIC DISEASES

Ursodeoxycholic acid has been studied in many cholestatic and noncholestatic liver diseases (11–13). Studies of the use of ursodeoxycholic acid in nonalcoholic steatohepatitis, an increasingly recognized cause of chronic

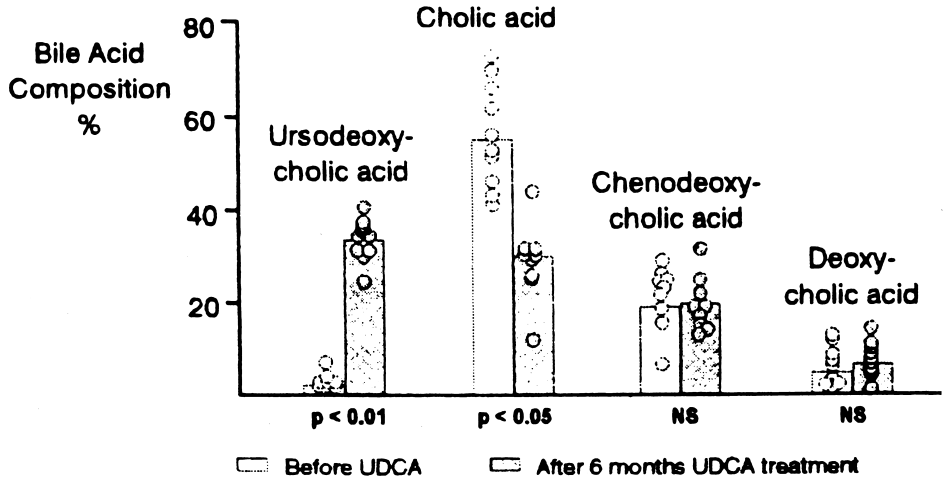

Figure 2. Relative proportions of the major conjugated bile acids (expressed as percentage of total conjugated bile acids) in the bile of patients with primary biliary cirrhosis before and after (**shaded**) 6 months of ursodeoxycholic acid treatment. Reprinted with permission from (9).

liver disease that may lead to cirrhosis and end-stage liver disease, are underway (14–16).

Primary Biliary Cirrhosis

Primary biliary cirrhosis is a disorder of unknown etiology that affects small- and medium-sized bile ducts within the liver. Progressive destruction of bile ducts leads to cholestasis and loss of ducts. Ultimately, patients may develop end-stage liver disease. Ursodeoxycholic acid has been studied extensively in this disease (3,11), using doses of 10 to 15 mg/kg/day. A combined analysis of three randomized trials of ursodeoxycholic acid in primary biliary cirrhosis from Canada, the United States, and France included more than 500 patients, with a median length of follow-up of approximately 4 years. Survival free of liver transplantation was significantly longer in the ursodeoxycholic acid group, with a 32% reduction in risk of death or transplantation (17,18). The benefit with ursodeoxycholic acid was greatest for patients with the most severe liver disease—those with elevated serum bilirubin levels and advanced liver damage in biopsy specimens. Based on these results and others (19), the Food and Drug Administration approved ursodeoxycholic acid (URSO; Axcan Pharma, Montreal, PQ, Canada) for the treatment of primary biliary cirrhosis. However, a recent meta-analysis of studies that used ursodeoxycholic acid to treat primary biliary cirrhosis did not show improvement in the end points of death or liver transplantation during the randomized phases of several clinical trials, although there may have been some benefit during the "switch-over" phase, when patients originally treated with placebo were given ursodeoxycholic acid (20).

Two recent studies suggest that ursodeoxycholic acid may lead to improvements in histologic evaluations of liver biopsy specimens in patients with primary biliary cirrhosis and that treatment may be cost-effective (21,22). Degott et al (21) showed that 4 years of ursodeoxycholic acid therapy was associated with a decrease in the prevalence of florid bile duct lesions and improvement in lobular inflammation and necrosis. Pasha et al (22) studied the costs and outcomes of treating patients who had primary biliary cirrhosis. The effectiveness of ursodeoxycholic acid was studied by comparing the rates of the development of complications of liver disease, such as ascites, variceal bleeding, liver transplantation, and death, in two placebo-controlled trials of ursodeoxycholic acid. Approximately twice as many complications occurred in the patients treated with placebo.

In summary, current data are inconclusive regarding the use of ursodeoxycholic acid in patients with primary biliary cirrhosis, given the lack of demonstrated benefit in reducing rates of liver transplantation and death (20). Ursodeoxycholic acid therapy may reduce the risk of esophageal varices in these patients (23), and improvement in pruritus and histologic findings have also been noted (19,24). The optimal dose of ursodeoxycholic acid is approximately 13 to 15 mg/kg/day in two or three divided doses. Some patients may not respond to therapy, as manifest by the absence of improvement in serum alkaline phosphatase and aminotransferase levels after several months of treatment. Combination therapy with immunosuppressive agents, such as methotrexate, is currently being studied (18).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis is a chronic liver disease associated with obstruction and stricture formation in

both small and large intra- and extrahepatic bile ducts. It can lead to progressive cholestasis with hepatic decompensation (25,26). There have been several randomized trials, involving more than 300 patients, of the use of ursodeoxycholic acid in this disease, including a large double-blind study in 105 patients. Although consistent improvements in serum alkaline phosphatase and bilirubin levels have been described, studies have not shown a benefit for ursodeoxycholic acid in reducing mortality or the need for liver transplantation (11,25–27).

There are several possible explanations for the lack of efficacy for ursodeoxycholic acid in primary sclerosing cholangitis. Because patients with this disease tend to be a more heterogeneous group than those with primary biliary cirrhosis, other therapies (such as endoscopic or percutaneous biliary drainage for dominant strictures) could affect outcomes. One study, for example, found that combined therapy involving the use of stents in dominant strictures as well as ursodeoxycholic acid led to improved survival free of liver transplantation compared with predicted rates; however, this study was not a randomized trial (28). It is also possible that the optimal dose of ursodeoxycholic acid in primary sclerosing cholangitis may need to be greater than in primary biliary cirrhosis.

Intrahepatic Cholestasis of Pregnancy

This disorder of unknown etiology typically develops in the second trimester of pregnancy. It is characterized by severe pruritus and jaundice and is associated with premature delivery and fetal demise (11,12). Serum bile acid, bilirubin, and aminotransferase levels may be elevated. Elevated bile acid concentrations in amniotic fluid and umbilical cord blood may account for the fetal complications (29). Clinical and biochemical abnormalities usually resolve a few weeks after delivery (30). The syndrome may be associated with progesterone therapy (31). Patients are at risk for recurrence with subsequent pregnancies or if they use oral contraceptives. In an open-label study, ursodeoxycholic acid therapy led to improvement in pruritus and serum aminotransferase levels (32).

In the only placebo-controlled trial, all infants born to women given ursodeoxycholic acid were born at or near term, and there were no stillbirths (33). In contrast, 5 of the 7 placebo-treated women delivered prematurely, including one still birth. No toxicity in either the mother or the fetus was observed. If confirmed in other studies, ursodeoxycholic acid may become an important treatment for cholestasis associated with pregnancy.

Graft-versus-Host Disease

Graft-versus-host disease is a major complication of bone marrow transplantation and has also been described in solid organ transplantation. It results from attack by donor T cells on immunodeficient recipient tissues displaying histocompatibility antigens. In the liver, the disorder is characterized by chronic cholestasis, leading to targeted destruction of intrahepatic bile ducts and eventually loss of bile ducts. Treatment has traditionally relied on increased immunosuppression. However, ursodeoxycholic acid therapy is a potential adjunctive treatment. In an open-label study in 13 patients, there was significant improvement in serum bilirubin, alkaline phosphatase, and aspartate aminotransferase levels during treatment (34).

Liver Disease Associated with Cystic Fibrosis

Cystic fibrosis is a genetic disease characterized by abnormal mucous gland secretion. It is caused by mutations in the gene for the cystic fibrosis transmembrane conductance regulator, a cAMP-dependent chloride channel in epithelial cells (35). The channel is also expressed on bile duct cells and can result in abnormal biliary secretion in patients with cystic fibrosis. Bile can become inspissated and intra- and extrahepatic cholestasis can develop, leading to cirrhosis and portal hypertension (12). Ursodeoxycholic acid therapy appears promising in the treatment of liver disease associated with cystic fibrosis. Treatment leads to improvement in serum γ-glutamyl transpeptidase and 5′-nucleotidase levels and appears to promote bile flow (36,37). Ursodeoxycholic acid may also be beneficial by stimulating chloride secretion in the gallbladder (38). In a randomized placebo-controlled trial in patients with liver disease resulting from cystic fibrosis, ursodeoxycholic acid was associated with an improvement in general well-being and nutritional status (36). High doses of ursodeoxycholic acid (20 mg/kg/day) are required (39).

Liver Disease Associated with Total Parenteral Nutrition

Patients treated with long-term total parenteral nutrition are at risk of developing liver disease, which may be transient or persistent, and which usually manifests as cholestatic abnormalities with elevations in serum alkaline phosphatase and bilirubin levels (12). The pathogenesis is unknown but may be related to changes in metabolism resulting from fasting, such as bile stasis related to lack of stimulation of bile flow. Histologic examination of affected livers can range from fatty change to severe steatohepatitis and fibrosis. Marked improvement in serum alkaline phosphatase levels after treatment with ursodeoxycholic acid was described in one report (40,41); trials are needed to confirm these initial findings.

Hepatic Allograft Rejection

Based on its anticholestatic and immunomodulatory properties, ursodeoxycholic acid has been studied as an adjunctive therapy to prevent rejection after liver transplantation. A preliminary study suggested that it may lead to improved serum alkaline phosphatase levels after liver transplantation and fewer episodes of rejection, as compared with historical controls (42). However, subsequent randomized trials failed to show a reduction in the num-

ber of rejection episodes, although one study found that fewer patients in the ursodeoxycholic acid group had more than one episode of rejection (43–45).

Nonalcoholic Steatohepatitis

This increasingly recognized entity, which accounts for a substantial proportion of liver disease seen in clinical practice, has histologic features that are similar to alcoholic liver disease. Progression to cirrhosis and end-stage liver disease appears to be less frequent than in alcoholic liver disease but has been described (15). Important risk factors for nonalcoholic steatohepatitis include obesity, diabetes mellitus, hypertriglyceridemia, and exposure to drugs or toxins (15). Jejunoileal bypass also appears to be associated with this disease (15). Ursodeoxycholic acid has been studied in preliminary studies and appears to be promising (15,16). A large, multicenter trial is currently underway.

Veno-occlusive Disease

A recent study suggests that ursodeoxycholic acid treatment might prevent hepatic veno-occlusive disease after bone marrow transplantation (46). This dreaded and often fatal complication of bone marrow transplantation has been attributed to toxicity from high-dose conditioning cytoreductive therapy. In a randomized, double-blind, placebo-controlled trial, patients who were treated with ursodeoxycholic acid at a dose of 600 to 900 mg daily had a 25% lower risk of veno-occlusive disease, hyperbilirubinemia, or ascites (46).

Miscellaneous Disorders

The hepatoprotective and immunomodulatory properties of ursodeoxycholic acid, coupled with its effects in promoting bile flow, make it an attractive potential adjunctive therapy in many chronic liver diseases that are associated with cholestasis, such as acute and chronic hepatitis, inborn errors of bile acid metabolism, and several pediatric liver diseases (47). Ursodeoxycholic acid does not appear to be effective in chronic hepatitis C. Although improvement in serum aminotransferase levels has been noted (48), ursodeoxycholic acid was not associated with enhanced clearance of hepatitis C virus RNA from the serum or with histologic improvement (49).

Toxicity

Ursodeoxycholic acid is associated with little, if any toxicity. The only side effect appears to be diarrhea, which probably occurs in less than 5% of patients (11,12,28). Because its absorption is enhanced by other bile acids, ursodeoxycholic acid should be taken with meals to promote bile acid secretion by the gallbladder (29).

SUMMARY AND CONCLUSIONS

Ursodeoxycholic acid, a hydrophilic bile acid, has potential as a therapeutic agent for several hepatobiliary diseases, especially cholestatic liver diseases. Although several studies found that its use improved outcomes in patients with primary biliary cirrhosis, other studies found no benefit, and a recent meta-analysis showed that its use did not reduce rates of liver transplantation or death. The favorable effects of ursodeoxycholic acid on liver injury associated with cholestasis, biliary secretion, and immune-mediated liver damage may be of therapeutic benefit in other liver diseases. Studies in patients with nonalcoholic steatohepatitis, chronic hepatitis, and other liver diseases are currently underway.

REFERENCES

1. Vlahcevic ZR, Heuman DM, Hylemon PB. Physiology and pathophysiology of enterohepatic circulation of bile acids. In: Zakim D, Boyer TD, eds. *Hepatology. A Textbook of Liver Disease*, 3rd ed. Philadelphia: WB Saunders, 1998:377–415.
2. Heuman DM. Quantitative estimation of the hydrophilic-hydrophobic balance of mixed bile salt solutions. *J Lipid Res*. 1989;30:719–730.
3. Beuers U, Boyer JL, Paumgartner G. Ursodeoxycholic acid in cholestasis: potential mechanisms of action and therapeutic applications. *Hepatology*. 1998;28:1449–1453.
4. Radominska A, Treat S, Little J. Bile acid metabolism and the pathophysiology of cholestasis. *Semin Liver Dis*. 1993;13:219–234.
5. Rubin RA, Kowalski TE, Khandelwal M, Malet PF. Ursodiol for hepatobiliary disorders. *Ann Intern Med*. 1994;121:207–218.
6. Hillaire S, Boucher E, Calmus Y, et al. Effects of bile acids and cholestasis on major histocompatibility complex class I in human and rat hepatocytes. *Gastroenterology*. 1994;107:781–788.
7. Crosignani A, Setchell KD, Invernizzi P, et al. Clinical pharmacokinetics of therapeutic bile acids. *Clin Pharmacokinet*. 1996;30:333–358.
8. Bachrach WH, Hofmann AF. Ursodeoxycholic acid in the treatment of cholesterol cholelithiasis (Part I). *Dig Dis Sci*. 1982;27:737–761.
9. Paumgartner G. Ursodeoxycholic acid treatment of primary biliary cirrhosis: potential mechanisms of action. In: Lindor KD, Heathcote EJ, Poupon R, eds. *Primary Biliary Cirrhosis: From Pathogenesis to Clinical Treatment*. Dordrecht: Kluwer Academic Publishers, 1998:138–146.
10. Guldutuna S, Zimmer G, Imhof M, et al. Molecular aspects of membrane stabilization by ursodeoxycholate. *Gastroenterology*. 1993;104:1736–1744.
11. Poupon RE, Chretien Y, Poupon R, Paumgartner G. Serum bile acids in primary biliary cirrhosis: effect of ursodeoxycholic acid therapy. *Hepatology*. 1993;17:599–604.
12. Calmus Y, Gane P, Rouger P, Poupon R. Hepatic expression of class I and class II major histocompatibility complex molecules in primary biliary cirrhosis: effect of ursodeoxycholic acid. *Hepatology*. 1990;11:12–15.
13. Cirillo NW, Zwas FR. Ursodeoxycholic acid in the treatment of chronic liver disease. *Am J Gastroenterol*. 1994;89:1447–1452.
14. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology*. 1994;107:1103–1109.
15. Sheth SG, Gordon FD, Chopra S. Nonalcoholic steatohepatitis. *Ann Intern Med*. 1997;126:137–145.
16. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23:1464–1467.

17. Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. *Gastroenterology*. 1997;113:884–890.
18. Angulo P, Lindor KD. Management of primary biliary cirrhosis and autoimmune cholangitis. *Clin Liver Dis*. 1998;2:333–351.
19. Emond M, Carithers RL Jr, Luketic VA, et al. Does ursodeoxycholic acid improve survival in patients with primary biliary cirrhosis? Comparison of outcome in the U.S. multicenter trial to expected survival using the Mayo Clinic prognostic model. *Hepatology*. 1996; 24:168A.
20. Goulis J, Leandro G, Burroughs AK. Randomised controlled trials of ursodeoxycholic-acid therapy for primary biliary cirrhosis: a meta-analysis. *Lancet*. 1999;354:1053–1060.
21. Degott C, Zafrani ES, Callard P, et al. Histopathological study of primary biliary cirrhosis and the effect of ursodeoxycholic acid treatment on histology progression. *Hepatology*. 1999;29:1007–1012.
22. Pasha T, Heathcote J, Gabriel S, et al. Cost-effectiveness of ursodeoxycholic acid therapy in primary biliary cirrhosis. *Hepatology*. 1999;29:21–26.
23. Lindor KD, Jorgensen RA, Therneau TM, et al. Ursodeoxycholic acid delays the onset of esophageal varices in primary biliary cirrhosis. *Mayo Clin Proc*. 1997;72:1137–1140.
24. Poupon RE, Balkau B, Eschwege E, Poupon R. A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. ursodeoxycholic acid-PBC Study Group. *NEJM*. 1991;324: 1548–1554.
25. Lee YM, Kaplan MM. Primary sclerosing cholangitis. *NEJM*. 1995; 332:924–933.
26. Mitchell SA, Chapman RWG. Management of primary sclerosing cholangitis. *Clin Liver Dis*. 1998;2:353–369.
27. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *NEJM*. 1997;336:691–695.
28. Stiehl A, Rudolph G, Sauer P, et al. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. *J Hepatol*. 1997;26:560–566.
29. Saksena S, Tandon RK. Ursodeoxycholic acid in the treatment of liver diseases. *Postgrad Med J*. 1997;73:75–80.
30. Reyes H. The enigma of intrahepatic cholestasis of pregnancy: lessons from Chile. *Hepatology*. 1982;2:87–96.
31. Bacq Y, Sapey T, Brechot MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. *Hepatology*. 1997;26:358–364.
32. Palma J, Reyes H, Ribalta J, et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. *Hepatology*. 1992;15:1043–1047.
33. Almuna R, Liepins J, Lira F, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol*. 1997;27:1022–1028.
34. Fried RH, Murakami CS, Fisher LD, et al. Ursodeoxycholic acid treatment of refractory chronic graft-versus-host disease of the liver. *Ann Intern Med*. 1992;116:624–629.
35. McGill JM, Kwiatkowski AP. Cholestatic liver diseases in adults. *Am J Gastroenterol*. 1998;93:684–691.
36. Colombo C, Battezzati PM, Podda M, et al. 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;23:1484–1490.
37. Colombo C, Castellani MR, Balistreri WF, et al. Scintigraphic documentation of an improvement in hepatobiliary excretory function after treatment with ursodeoxycholic acid in patients with cystic fibrosis and associated liver disease. *Hepatology*. 1992;15:677–684.
38. Shimokura GH, McGill JM, Schlenker T, Fitz JG. Ursodeoxycholate increases cytosolic calcium concentration and activates Cl-currents in a biliary cell line. *Gastroenterology*. 1995;109:965–972.
39. Colombo C, Crosignani A, Assaisso M, et al. Ursodeoxycholic acid therapy in cystic fibrosis-associated liver disease: a dose-response study. *Hepatology*. 1992;16:924–930.
40. Lindor KD, Burnes J. Ursodeoxycholic acid for the treatment of home parenteral nutrition-associated cholestasis. A case report. *Gastroenterology*. 1991;101:250–253.
41. Beau P, Labat-Labourdette J, Ingrand P, Beauchant M. Is ursodeoxycholic acid an effective therapy for total parenteral nutrition-related liver disease? *J Hepatol*. 1994;20:240–244.
42. Friman S, Persson H, Schersten T, et al. Adjuvant treatment with ursodeoxycholic acid reduces acute rejection after liver transplantation. *Transplant Proc*. 1992;24:389–390.
43. Pageaux GP, Blanc P, Perrigault PF, et al. Failure of ursodeoxycholic acid to prevent acute cellular rejection after liver transplantation. *J Hepatol*. 1995;23:119–122.
44. Keiding S, Hockerstedt K, Bjoro K, et al. The Nordic multicenter double-blind randomized controlled trial of prophylactic ursodeoxycholic acid in liver transplant patients. *Transplantation*. 1997; 63:1591–1594.
45. Barnes D, Talenti D, Cammell G, et al. A randomized clinical trial of ursodeoxycholic acid as adjuvant treatment to prevent liver transplant rejection. *Hepatology*. 1997;26:853–857.
46. Essell JH, Schroeder MT, Harman GS, et al. Ursodiol prophylaxis against hepatic complications of allogeneic bone marrow transplantation. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128:975–981.
47. Poupon R, Poupon RE. Ursodeoxycholic acid therapy of chronic cholestatic conditions in adults and children. *Pharmacol Ther*. 1995;66:1–15.
48. Crosignani A, Budillon G, Cimino L, et al. Tauroursodeoxycholic acid for the treatment of HCV-related chronic hepatitis: a multicenter placebo-controlled study. *Hepatogastroenterology*. 1998;45: 1624–1629.
49. Abdelmalek MF, Harrison ME, Gross JB Jr, et al. Treatment of chronic hepatitis C with interferon with or without ursodeoxycholic acid: a randomized prospective trial. *J Clin Gastroenterol*. 1998;26:130–134.