CME CREDIT

Primary biliary cirrhosis: Ursodiol effective, but think transplantation sooner

ROBERT L. CARITHERS, JR, MD

Professor of medicine, director of the hepatology section, and medical director of the liver transplantation program, University of Washington, Seattle; investigator, US multicenter study on ursodiol therapy for primary biliary cirrhosis.

ABSTRACT

Ursodiol may slow the progression of primary biliary cirrhosis, but treatment is still mainly palliative, and liver transplantation is the only definitive therapy.

Follow up stable patients every 6 to 12 months

UNTIL RECENTLY, there was no therapy for delaying the progression of primary biliary cirrhosis. Now, studies have shown the anti-gallstone drug ursodiol to be safe and probably effective for delaying transplantation and improving survival in patients with primary biliary cirrhosis. Nevertheless, liver transplantation remains the only definitive treatment. Physicians should think about refering their patients to a transplant center early, because patients are often closer to liver failure than their signs, symptoms, and laboratory results seem to indicate, and because of the long waiting list for liver transplants.

FEATURES OF PRIMARY BILIARY CIRRHOSIS

Primary biliary cirrhosis is a cholestatic disease distinct from alcoholic cirrhosis. The etiology is unknown but is believed to be autoimmune. Approximately 90% of cases occur in women, usually in middle age. Pruritus is a major symptom; many patients also experience fatigue. Many patients also have Sjögren-like symptoms of dry mouth and eyes; a few have the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia).

Laboratory abnormalities. The alkaline phosphatase level is elevated in approximately 90% of cases. Also in 90%, antimitochondrial antibody is present. Most patients have increased IgM levels. Liver biopsy is diagnostic, showing well-defined stages of autoimmune destruction of the small intrahepatic bile ducts.[1]

Complications. Many patients experience osteoporosis, which can lead to vertebral and hip fractures; patients are especially vulnerable in the period immediately following transplantation when they are taking corticosteroids. For unknown reasons, patients also have an increased risk of breast cancer and urinary tract infections. Some patients have deficiencies of the fat-soluble vitamins (A, D, E, K) and some minerals (zinc, calcium).

TREATING THE SYMPTOMS AND COMPLICATIONS

Until ursodiol was introduced, treatment for primary biliary cirrhosis consisted of preventing and alleviating the symptoms and complications, as no therapies aimed at altering the course of the disease were both safe and effective. Even now, palliation constitutes a large part of the primary physician's task.

Pruritus usually can be controlled with cholestyramine 8 g, three to four times a day before meals.

Deficiency of the fat-soluble vitamins A, D, E, and K, due to malabsorption, should be monitored and replaced as necessary. Supplemental zinc can be given orally.

URSODIOL THERAPY FOR PRIMARY BILIARY CIRRHOSIS

Four large trials[2–5] of ursodiol therapy in primary biliary cirrhosis had somewhat differing patient populations, methods, and findings, and none of them had the statistical power to

make any conclusions about patient survival. Nevertheless, taken together, the results seem to indicate that this drug:

- Dramatically decreases the elevated liver enzyme levels in this disease (but has no effect on low serum albumin levels or elevated prothrombin times);
- Possibly relieves symptoms, especially pruritus;
- Possibly arrests the histological changes in the liver (but does not reverse fibrosis, the end histologic stage)[6];
- Probably prolongs overall survival and survival free of transplantation[7–11];
- Is safe and has a low side-effect profile, the principal side effect being diarrhea.

It is anticipated that ursodiol will be approved by the FDA for the treatment of patients with primary biliary cirrhosis later this year.

Dosage. 15 mg/kg daily at bedtime or in divided doses.

Combination therapy. Ursodiol has been combined with colchicine,[12,13] prednisolone,[14] and methotrexate[15] in clinical trials and shows some promise. However, combination treatment should be limited to carefully controlled clinical trials until the benefits and toxicity are well defined.

REFER FOR TRANSPLANTATION EARLIER RATHER THAN LATER

Primary biliary cirrhosis usually progresses to end-stage liver failure and death or transplantation, but the rate of progression varies considerably. Stable patients should be seen every 6 to 12 months for follow-up.

Using a large database of cases from the era before transplantation, investigators at the Mayo Clinic devised a prognostic scale based on five factors: serum bilirubin level, serum albumin level, age, prothrombin time, and edema (TABLE 1).[16] This scale has been well validated, and physicians can and should use it in deciding when to refer patients for liver transplantation,[17] even after introduction of ursodiol therapy (which reduces the bilirubin level).[8]

The results are sometimes surprising. For example, suppose a 55-year-old patient has a serum bilirubin level of 4.0 mg/dL, a serum albumin level of 3.1 g/dL, and a prothrombin

TABLE 1

How to calculate the chances of survival in primary biliary cirrhosis

1. Add the following to find the risk score:

Bilirubin: 4.0 mg/dL
Use a calculator to find the natural logarithm (loge) of this number, and then multiply by 0.871 → 1.2

Albumin: 3.1 g/dL
Find loge of this number and then multiply by – 2.53 → -2.9

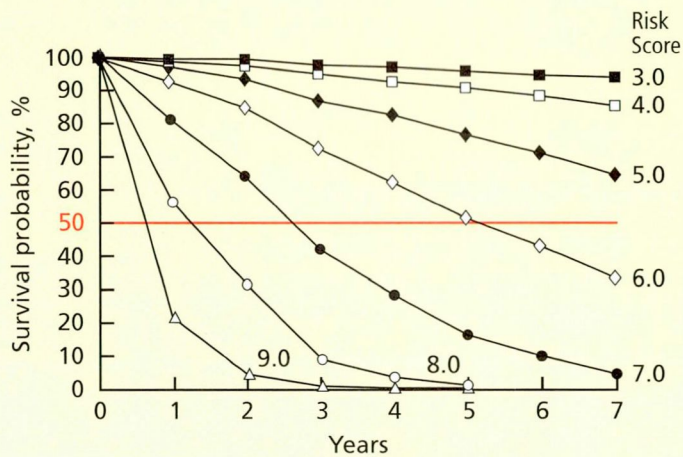
Age: 55 years
Multiply this number by 0.039 → 2.2

Prothrombin time: 14 seconds
Find loge of this number and then multiply by 2.38 → 6.3

Edema score: 0.5 (see below)
0 No edema, no diuretic therapy
0.5 Edema without diuretic therapy, or edema resolved with diuretic therapy
1.0 Edema despite diuretic therapy
Multiply this number by 0.859 → 0.4

RISK SCORE = 7.2

2. Compare risk score with the survival curves below:



SOURCE: FORMULA FROM DICKSON ET AL, REFERENCE 16; GRAPH FROM WIESNER ET AL, REFERENCE 17

time of 14 seconds; she has edema and is not taking a diuretic. A physician might mistakenly assume that this patient is not very sick. Yet, her risk score is 7.2, indicating that without transplantation her chances of surviving 2 years are little better than 50%, and her chances of surviving 7 years are practically nil.

Patients should be referred for transplantation when their 1-year chance of survival falls below 90%, ie, when their risk score is 6 or higher. An even simpler rule of thumb is to refer when the bilirubin level increases to 2 mg/dL or higher. Although such patients may seem well, the typical waiting time for a transplant is 1 to 2 years, by which time their risk scores will be higher.

Transplantations are ideally performed when the risk score is between 7 and 9. Patients with scores over 10 tend to have poor outcomes after transplantation.[18] Only 3,500 to 4,000 donor livers are available in the entire United States per year; therefore, at some point we as a nation will have to recognize that some patients are too sick for transplantation, and to use this scarce resource optimally, we will have to reserve transplantation for patients with lower risk scores.

Refer for a transplant at a risk score ≥ 6 bilirubin ≥ 2

REFERENCES

1. **Ludwig J, Dickson ER, McDonald GSA.** Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). Virchows Arch Pathol Anat 1978; 379:103–112.
2. **Poupon RE, Balkau B, Eschwege E, et al.** A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis. N Engl J Med 1991; 324:1548–1554.
3. **Heathcote EJ, Cauch-Dudek K, Walker V, et al.** The Canadian multicenter double-blind randomized controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1994; 19:1149–1156.
4. **Lindor KD, Dickson ER, Baldus WP, et al.** Ursodeoxycholic acid in the treatment of primary biliary cirrhosis. Gastroenterol 1994; 106:1284–1290.
5. **Combes B, Carithers RL Jr, Maddrey WC, et al.** A randomized, double-blind, placebo-controlled trial of ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1995; 22:759–766.
6. **Batts KP, Jorgensen RA, Dickson ER, et al.** Effects of ursodeoxycholic acid on hepatic inflammation and histologic stage in patients with primary biliary cirrhosis. Am J Gastroenterol 1996; 91:2314–2317.
7. **Poupon RE, Poupon R, Balkau B, et al.** Ursodiol for the long-term treatment of primary biliary cirrhosis. N Engl J Med 1994; 330:1342–1347.
8. **Kilmurry MR, Heathcote EJ, Cauch-Dudek K, et al.** Is the Mayo model for predicting survival useful after the introduction of ursodeoxycholic acid treatment for primary biliary cirrhosis? Hepatology 1996; 23:1148–1153.
9. **Carithers RL Jr, Luketic VA, Peters M, et al.** Extended follow-up of patients in the US multicenter trial of ursodeoxycholic acid for primary biliary cirrhosis (abstract). Gastroenterol 1996; 110:A1163.
10. **Lindor KD, Therneau TM, Jorgensen RA, et al.** Effects of ursodeoxycholic acid on survival in patients with primary biliary cirrhosis. Gastroenterol 1996; 110:1515–1518.
11. **Poupon RE, Lindor KD, Cauch-Dudek K, et al.** Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterol 1997; 113:884–890.
12. **Ikeda T, Tozuka S, Noguchi O, et al.** Effects of additional administration of colchicine in ursodeoxycholic acid-treated patients with primary biliary cirrhosis: a prospective randomized study. J Hepatol 1996; 24:88–94.
13. **Poupon RE, Huet PM, Poupon R, et al.** A randomized trial comparing colchicine and ursodeoxycholic acid combination to ursodeoxycholic acid in primary biliary cirrhosis. Hepatology 1996; 24:1098–1103.
14. **Leuschner M, Guldutuna S, You T, et al.** Ursodeoxycholic acid and prednisolone versus ursodeoxycholic acid and placebo in the treatment of early stages of primary biliary cirrhosis. J Hepatol 1996; 25:49–57.
15. **Lindor KD, Dickson ER, Jorgensen RA, et al.** The combination of ursodeoxycholic acid and methotrexate for patients with primary biliary cirrhosis: the results of a pilot study. Hepatology 1995; 22:1158–1162.
16. **Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A.** Prognosis in primary biliary cirrhosis: Model for decision making. Hepatology 1989; 10:1–7.
17. **Wiesner RH, Porayko MK, Dickson ER, et al.** Selection and timing of liver transplantation in primary biliary cirrhosis and primary sclerosing cholangitis. Hepatology 1992; 16:1290–1299.
18. **Markus BH, Dickson ER, Grambsch PM, et al.** Efficacy of liver transplantation in patients with primary biliary cirrhosis. N Engl J Med 1989; 320:1709–1713.

Diagnosing Marfan syndrome is still based on clinical characteristics

DOUGLAS S. MOODIE, MD

Chairman, Department of Pediatrics, Cleveland Clinic; currently caring for about 450 Marfan syndrome patients.

ABSTRACT

Despite new genetic findings, the best way to diagnose Marfan syndrome is still the classic clinical manifestations.

PHYSICIANS WILL HAVE TO CONTINUE to rely on clinical findings—family history, tall slender habitus, ocular abnormalities, and potentially fatal cardiac abnormalities—in diagnosing Marfan syndrome, even though investigators recently identified the gene that, if defec-