

CLINICAL THERAPEUTICS

Ursodeoxycholic Acid for the Treatment of Primary Biliary Cirrhosis

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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A 52-year-old woman presents with a 1-year history of fatigue and itching. Several months before presentation, her primary care physician noted abnormal liver-function tests, and levels have been persistently elevated since that time. A test for anti-mitochondrial antibodies was positive. During a pregnancy several years earlier, a test for antinuclear antibodies was also positive. The patient has severe fatigue and occasional pruritus. She reports having had no jaundice or gastrointestinal bleeding. The physical examination and ultrasonography of the liver and biliary tree show no abnormalities. A liver biopsy shows stage I primary biliary cirrhosis. Treatment with ursodeoxycholic acid is recommended.

THE CLINICAL PROBLEM

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Primary biliary cirrhosis is a chronic cholestatic liver condition that primarily affects middle-aged women.^{1,2} The prevalence in the United States is estimated at about 150 cases per million persons but may be as high as 400 per million among women.^{3,4} Patients with the disease, when symptomatic, often present with fatigue and pruritus. Findings on examination can include hepatosplenomegaly and hyperpigmentation; jaundice is a late manifestation. Primary biliary cirrhosis may be associated with other autoimmune conditions, as well as some unique complications of cholestasis, such as osteoporosis and hypercholesterolemia.⁵⁻⁷

The most common cause of death in patients with primary biliary cirrhosis is liver failure. The disease at one time was the leading indication for liver transplantation, but effective therapy has reduced the need for transplantation in this group of patients as well as improving life expectancy.⁸⁻¹⁰ At one time, the median survival was approximately 10 years, but now, survival may approach a normal life span if treatment is begun early.¹¹

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

Primary biliary cirrhosis appears to be a classic autoimmune disease in which a variety of environmental toxins or infectious agents, including viruses, bacteria, and chemicals, may trigger an immune response that becomes self-perpetuating.¹²⁻¹⁴ Genetic susceptibility is suggested by the increased frequency of primary biliary cirrhosis among first-degree relatives of index patients^{15,16} and by the association with certain HLA haplotypes.¹⁷

Antimitochondrial antibodies are characteristic of primary biliary cirrhosis and are found in at least 95% of patients.¹ The specific epitopes with which these anti-

bodies react are found on enzymes in the inner mitochondrial membrane, although it is still unclear whether antimitochondrial antibodies are involved in the pathogenesis of the disease or are merely markers of the inflammatory process.¹⁸⁻²⁰ Recently, animal models have suggested a direct role of antimitochondrial antibodies in the pathogenesis of the disease, but this finding remains somewhat controversial.²¹⁻²³ A T-cell-mediated response has also been implicated.¹⁷ Since mitochondria are found in all cells, the specificity of the immune response in primary biliary cirrhosis (which principally targets bile-duct epithelium) remains unexplained.

The eventual outcome of the immune reaction in primary biliary cirrhosis is the destruction of small intralobular bile ducts with resultant cholestasis (Fig. 1). Cholestasis begets liver injury directly, causing inflammation and necrosis. Retained bile acids may cause damage to hepatocytes and increased expression of HLA antigens on hepatocytes, thereby enhancing the autoimmune response.²⁴ The disease is classified into four stages of severity on the basis of histologic findings on liver biopsy (Table 1).

Ursodeoxycholic acid, a bile acid with fewer hepatotoxic properties than endogenous bile acids, competes with the endogenous bile acids for absorption in the terminal ileum.²⁵ Eventually, with therapy, ursodeoxycholic acid will become the predominant bile acid, accounting for up to 40% or 50% of the total bile-acid pool.²⁶ The mechanism of action of ursodeoxycholic acid is uncertain and is probably multifactorial. It appears to promote the endogenous secretion of bile acid and to reduce the cytotoxic potential of endogenous bile acids, altering and reducing inflammatory cytokine production, protecting cell membranes from disruption, and reducing the display of aberrant HLA antigens.²⁷⁻²⁹

CLINICAL EVIDENCE

At least a dozen studies have compared ursodeoxycholic acid for the treatment of primary biliary cirrhosis with placebo. Although a recent meta-analysis of these trials did not suggest a beneficial effect of treatment with ursodeoxycholic acid on rates of death or liver transplantation,³⁰ some of the studies used what are now considered to be inadequate doses of ursodeoxycholic acid or too short a period of follow-up.^{8,31-36}

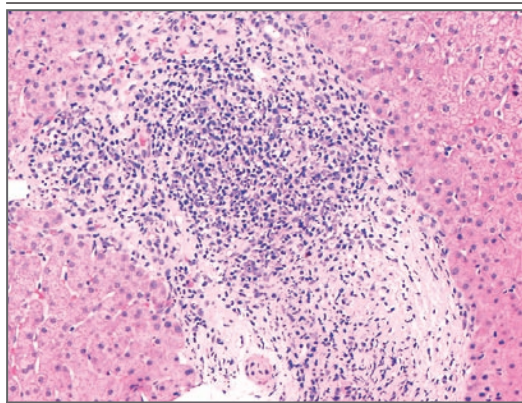


Figure 1. Liver-Biopsy Specimen Showing Stage I Primary Biliary Cirrhosis.

A portal area shows an expansile infiltrate of mixed chronic inflammatory cells that obliterates the bile duct and is not associated with substantial periportal spillover. Occasional bile ductules are present at the periphery. There is a mild degree of portal fibrosis without substantial periportal fibrosis (hematoxylin and eosin).

Table 1. Histologic Staging of Primary Biliary Cirrhosis.

Stage	Histologic Findings
I	Inflammation in the portal space
II	Inflammation extending into the hepatic parenchyma
III	Septal or bridging fibrosis
IV	Cirrhosis with regenerative nodules

A meta-analysis that was confined to trials using an appropriate dose of ursodeoxycholic acid (>10 mg per kilogram of body weight per day) and with sufficient follow-up (at least 2 years) included a total of 1038 patients (522 who received ursodeoxycholic acid and 516 who received placebo).⁹ Treatment with ursodeoxycholic acid resulted in significant improvement in liver biochemical values. Histologic evidence of disease progression was similar for the two treatment groups, but subjects without evidence of fibrosis (stages I and II) who were treated with ursodeoxycholic acid had slower disease progression than did subjects in the control group. A total of 160 patients who were treated with ursodeoxycholic acid and 186 control subjects died or underwent liver transplantation. This difference was significant in a fixed-effect model (odds ratio, 0.76; 95% confidence interval [CI], 0.57 to 1.00; $P=0.05$) but not

in a random-effects model (odds ratio, 0.77; 95% CI, 0.50 to 1.21; $P=0.30$), although the odds ratios for both models suggest a clinically important treatment effect that was not significant because of an insufficient number of patients.

Other agents, including colchicine, methotrexate, penicillamine, azathioprine, and cyclosporine, have been tested for the treatment of primary biliary cirrhosis but appear to lack beneficial effects similar to those of ursodeoxycholic acid.³⁷⁻⁴¹ There have been very few head-to-head comparisons of ursodeoxycholic acid with other agents, aside from studies comparing ursodeoxycholic acid alone with the agent in combination with another drug. None of these studies have shown that combination therapy was superior to ursodeoxycholic acid alone.

CLINICAL USE

The use of ursodeoxycholic acid has been recommended for patients with primary biliary cirrhosis who have positive tests for antimitochondrial antibodies and elevated liver biochemical markers (typically in a cholestatic pattern).⁴² Some patients with primary biliary cirrhosis have positive tests for antimitochondrial antibodies but have normal liver enzyme levels; these patients may eventually have clinical manifestations of primary biliary cirrhosis (including histologic changes)⁴³ but are not considered candidates for any therapy.⁴²

A liver biopsy is not essential for either the diagnosis of primary biliary cirrhosis or the initiation of treatment. Although therapy with ursodeoxycholic acid is most effective in patients with stage I or II disease, patients at any stage of disease are candidates for such therapy. In fact, patients with advanced-stage disease who were treated with ursodeoxycholic acid while they were awaiting liver transplantation did at least as well as, if not better than, patients who did not receive the medication.⁴⁴ At present, many patients do not undergo liver biopsy before starting treatment with ursodeoxycholic acid.

The dose of ursodeoxycholic acid appears to be important. A study comparing three different doses showed that a dose of 13 to 15 mg per kilogram of body weight per day appeared to be optimal, as compared with doses of either 5 to 7 mg or 23 to 25 mg.⁴⁵ The lower dose was not as effective in improving liver biochemical markers, and the higher dose was no more effective

than the intermediate dose. Doubling the dose for patients with a suboptimal response did not appear to offer benefit, and timing of administration did not seem to be vital.⁴⁶ Some studies initially used a regimen of administration three or four times a day, but it has been shown that a regimen of once or twice a day provides equivalent results. Anecdotal experience at the Mayo Clinic suggests that initiation of the drug at the full dose may precipitate pruritus and loose stool, but a gradual initiation of the drug over a period of 1 to 2 weeks eliminates these problems. Thus, for example, therapy might be started at a dose of 250 mg per day with an increase in the dose every 3 to 4 days until the target dose of 13 to 15 mg per kilogram per day is reached.

The choice of drug formulation has not been directly tested in patients with primary biliary cirrhosis. The only available data come from short-term trials involving normal volunteers, in which there appear to have been substantial differences in bioavailability on the basis of the preparation.⁴⁷ However, I am not aware of any attempt to replicate these findings in patients with primary biliary cirrhosis who have had long-term treatment. The drug in the short-term trial with the best rate of absorption (Urso 250-mg or 500-mg tablets, Axcan Pharma) is the only ursodiol formulation approved by the Food and Drug Administration for the treatment of primary biliary cirrhosis.

There are a few drugs that have important interactions with ursodeoxycholic acid; these include clofibrate, cholestyramine, and other cholesterol-binding or bile acid-binding sequestrants. Estrogens may increase biliary cholesterol levels, whereas charcoal and some antacids may bind bile acids. The dose of ursodeoxycholic acid does not have to be adjusted for renal or other hepatic diseases.

Results of therapy can be monitored through the analysis of liver biochemical values. An initial response will be seen within a month to 6 weeks. Approximately 80 to 90% of full improvement will occur within 3 months. Normalization of biochemical values will occur within 2 years in 20% of patients⁴⁸; such normalization will occur in an additional 15% of patients after 5 years. A rapid initial response is typically followed by slow, continued improvement.⁴⁸ No other follow-up testing needs to be done, and liver biopsy is not routinely repeated to assess the effect of therapy.

Studies have shown that the clinical and bio-

chemical response to ursodeoxycholic acid can be used to predict the long-term outcome. The Mayo Risk Score, which incorporates the patient's age, total levels of bilirubin and albumin, the prothrombin time, and the presence or absence of edema and ascites, can be calculated after 6 months of ursodiol therapy to provide an accurate prediction of life expectancy.⁴⁹ (An online tool for calculating the Mayo Risk Score is available at www.mayoclinic.org/gi-rst/mayomodel1.html.) In a similar manner, the response of alkaline phosphatase to treatment may provide a useful estimate of prognosis. In one study, patients with a decrease in the level of alkaline phosphatase of at least 40% or a decrease to the normal range at 1 year had a prognosis similar to that of an age-matched healthy population.⁵⁰

Treatment with ursodeoxycholic acid is relatively expensive. The average wholesale price per tablet in the Thomson Healthcare 2007 Red Book was \$2.47 for Urso 250, \$4.65 for Urso 500, and \$2.57 for generic ursodiol (300 mg). If patients stop taking the drug (as happened in the late 1990s, when the drug was unavailable in the United States and Canada), liver biochemical markers will return to baseline values. Fortunately, reintroducing the drug will usually result in a treatment response that is similar to the initial effect. This inadvertent experience has shown that treatment with ursodeoxycholic acid needs to be continued on a long-term basis, and life-long therapy is currently recommended.

The management of primary biliary cirrhosis should also include appropriate therapy of related complications, since ursodeoxycholic acid alone does not have a significant effect on all of the associated conditions. Elevated lipid levels (particularly elevated levels of low-density lipoprotein cholesterol) can be reduced with ursodeoxycholic acid, but additional treatment with lipid-lowering agents such as cholestyramine or statins is sometimes administered.^{51,52} Osteoporosis can be treated with calcium and bisphosphonates.^{2,53} Pruritus can be reduced by various means, including the use of antihistamines, cholestyramine, rifampin, and opioid antagonists.²

ADVERSE EFFECTS

The most commonly reported adverse effect of ursodeoxycholic acid is weight gain, which averages approximately 5 lb (2.3 kg) during the first

1 to 2 years.⁵⁴ This increase in weight is not progressive. Some patients have reported thinning of the hair, although this symptom is not well described in the literature and is relatively uncommon. Loose stools have been reported infrequently.

AREAS OF UNCERTAINTY

As noted above, ursodeoxycholic acid is currently used in patients with primary biliary cirrhosis who have abnormal liver biochemical values. It remains uncertain whether patients with antimitochondrial antibodies but with normal liver-function markers would benefit from treatment.^{42,43}

The majority of patients who are treated with ursodeoxycholic acid have ongoing liver biochemical abnormalities, which in some cases may point to a poorer prognosis. Combinations of ursodeoxycholic acid with other agents have been tested in an effort to enhance the efficacy of treatment. The role of these combination regimens remains unclear because none of them have been shown to be beneficial in controlled trials.

Colchicine, which has been used for many years as a single agent in the treatment of primary biliary cirrhosis, does not appear to have a significant effect on either survival or the need for liver transplantation.³⁷ However, in a trial comparing low-dose ursodeoxycholic acid (500 mg per day) alone with ursodeoxycholic acid plus colchicine, the combined regimen was associated with fewer treatment failures and an improvement in liver histologic features.⁵⁵ Extension of the study for up to 10 years did not confirm this benefit.⁵⁶

Methotrexate has also been used extensively in the management of primary biliary cirrhosis. However, a meta-analysis of trials of this agent showed no evidence of a benefit and a suggestion of harm in this setting.⁵⁷ A 10-year randomized, controlled trial comparing ursodeoxycholic acid plus methotrexate with ursodeoxycholic acid plus colchicine showed similar transplantation-free survival in the two study groups, with a prognosis similar to that predicted by the Mayo Risk Score. There was evidence of biochemical and histologic improvement among patients who continued to receive their assigned therapy for the duration of the trial.⁵⁸

Recent studies have described a subgroup of patients with primary biliary cirrhosis who have

features that overlap with those of autoimmune hepatitis. These patients may have more aggressive disease and may be candidates for more aggressive immunosuppressive therapy, but this hypothesis remains only conjectural at this time.⁵⁹

GUIDELINES

The practice guidelines of the American Association for the Study of Liver Diseases state that appropriately selected patients with primary biliary cirrhosis and abnormal liver biochemical values should be advised to take ursodeoxycholic acid at a dose of 13 to 15 mg per kilogram daily either in divided doses or as a single daily dose. If cholestyramine is used, 4 hours should elapse between the administration of cholestyramine and that of ursodeoxycholic acid.⁴²

RECOMMENDATIONS

The patient in the vignette meets the clinical and histologic criteria for the diagnosis of primary biliary cirrhosis. Because she has this diagnosis and has elevated liver biochemical values, she is an appropriate candidate for treatment with ursodeoxycholic acid. A dose of 13 to 15 mg per kilogram per day should be provided, with slow initiation (one 250-mg tablet given daily for 3 to 4 days, with successive tablets added at intervals of 3 to 4 days). Monitoring of liver biochemical values should be performed at 3-month intervals. It is not necessary to repeat the liver biopsy.

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