Progression of Primary Biliary Cirrhosis With Ursodeoxycholic Acid Therapy

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Three patients with symptomatic, noncirrhotic primary biliary cirrhosis who had no evidence of esophageal varices on esophagogastroduodenoscopy and who were treated with ursodeoxycholic acid, 15 mg·kg⁻¹·day⁻¹, for a period of 1–2 years are reported. Initially, all three patients showed improvement in symptoms of fatigue and pruritus, and there was marked improvement or normalization in serum levels of bilirubin, alkaline phosphatase, and alanine aminotransferase. However, after 1–2 years, all three patients progressed histologically to cirrhosis on follow-up liver biopsy, and all had esophageal variceal bleeding documented by esophagogastroduodenoscopy. These three patients represent examples of ursodeoxycholic acid treatment failure despite improvements in symptoms and biochemical liver test results.

Case Report

Case 1

In January 1988, a 63-year-old white woman was referred to the Mayo Clinic for fatigue, mild pruritus, and anorexia of 5 months' duration. There was no history of liver disease, heavy alcohol ingestion, blood transfusions, or exposure to hepatitis or hepatotoxins. The physical examination revealed increased skin pigmentation with no clinical evidence of ascites, splenomegaly, or peripheral edema. Results of biochemical liver tests were consistent with cholestasis (Table 1). The anti-mitochondrial antibody (AMA) was positive in a titer of 1:640, and hepatitis A, B, and C serologies were negative. Results of a screening esophagogastroduodenoscopy (EGD) were negative for esophageal and gastric varices. Results of abdominal ultrasonography were normal, and an endoscopic retrograde cholangiogram revealed normal intrahepatic and extrahepatic bile ducts. A transthoracic needle biopsy of the liver (2.6-cm tissue core) showed morphological features compatible with PBC (histological stage 2, Ludwig classification).

The patient was begun on UDCA therapy, 15 mg·kg⁻¹·day⁻¹. Within 1 month, she had a decrease in fatigue and pruritus and improvement in results of biochemical liver tests including serum levels of bilirubin, alkaline phosphatase, aminotransferases, and γ-glutamyl transferase. Furthermore, results of some studies have suggested that UDCA therapy might be associated with histological stabilization or improvement.

However, whereas some studies have shown that UDCA therapy may have a beneficial effect in PBC, others have suggested that this effect is temporary and that UDCA has no major effect in preventing histological progression. Thus, the efficacy of UDCA therapy in PBC must be considered indeterminate at this time.
Table 1. Clinical Findings and Biochemical Indicators of Liver Function Patients With PBC Before and After Treatment With UDCA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>6 mo</td>
<td>1 yr</td>
</tr>
<tr>
<td>Bilirubin (µmol/L [mg/dL])</td>
<td>70</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>(4.1)</td>
<td>(2.5)</td>
<td>(1.9)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>527</td>
<td>282</td>
<td>267</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>76</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>Albumin (g/L [g/dL])</td>
<td>29</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>(2.9)</td>
<td>(3.1)</td>
<td>(3.0)</td>
</tr>
<tr>
<td>Ascites</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Esophageal variceal bleed</td>
<td>No</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Histological stagea</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

aNormal limits: bilirubin, <19 µmol/L (<1.1 mg/dL); alkaline phosphatase, <250 U/L; alanine aminotransferase, <31 U/L; albumin, >35 g/L (>3.5 g/dL).

bAccording to the Ludwig classification.14

presence of a fluid wave and shifting dullness. Ultrasonography revealed the presence of ascites and splenomegaly, and a repeat liver biopsy confirmed the presence of biliary cirrhosis (PBC histological stage 4). The patient has subsequently undergone liver transplantation.

Case 2

In May 1988, a 69-year-old white woman was referred to the Mayo Clinic for fatigue, pruritus, and weight loss of several months’ duration. Additionally, there was a history of Raynaud’s phenomenon and keratoconjunctivitis sicca. There was no history of liver disease, heavy alcohol ingestion, blood transfusions, or exposure to hepatitis or hepatotoxins.

On physical examination, the skin was moderately pigmented, but there were no ascites, peripheral edema, or splenomegaly. Laboratory testing suggested the presence of cholestasis (Table 1). AMA was positive at a titer of 1:640, and serologies for hepatitis B and C were negative. An EGD revealed the absence of esophageal and gastric varices. Transthoracic liver biopsy (2.5 cm tissue core) revealed several florid duct lesions and other morphological features compatible with PBC (histological stage 2).

The patient was begun on UDCA therapy, 15 mg·kg⁻¹·day⁻¹, after which she showed initial clinical improvement in her fatigue and pruritus. Results of biochemical liver tests also improved (Table 1). However, after almost 2 years of therapy, the patient was admitted to a local hospital for hematemesis and syncope. An EGD confirmed the presence of bleeding esophageal varices, and the patient underwent sclerotherapy. Ultrasonography showed the presence of splenomegaly, and a repeat liver biopsy performed 2 months later (2.6 cm tissue core) confirmed the presence of PBC (histological stage 4). The patient is currently being evaluated for liver transplantation because chronic sclerotherapy has failed to control her variceal bleeding.

Case 3

In June 1988, a 60-year-old white woman was referred to the Mayo Clinic for pruritus and fatigue of 3 months’ duration. There was no history of heavy alcohol ingestion, blood transfusions, or exposure to hepatitis or hepatotoxins.

Results of physical examination were negative for stigmata of chronic liver disease, hepatosplenomegaly, ascites, and peripheral edema. Biochemical liver tests suggested the presence of cholestasis (Table 1). Her AMA was positive in a titer of 1:1280, and hepatitis B and C serologies were negative. Results of ultrasonography of the liver were normal, and an EGD revealed no evidence of esophageal or gastric varices. A transthoracic liver biopsy (2.4 cm tissue core) was performed revealing histological features compatible with PBC (histological stage 3). The patient was begun on UDCA therapy (15 mg·kg⁻¹·day⁻¹), and after 6 months of therapy, complete resolution of pruritus and fatigue, along with marked improvement in biochemical liver test results, was noted (Table 1). One year after beginning therapy, the patient again noted pruritus and fatigue. One month later, she was admitted to a local hospital because of hematemesis and syncope. An EGD confirmed the presence of bleeding esophageal varices, which were treated with sclerotherapy. Ultrasonography revealed the presence of splenomegaly and ascites, and a repeat transthoracic needle biopsy of the liver (2.7 cm tissue core) confirmed the presence of PBC (histological stage 4). The patient subsequently had further variceal bleeding and is now awaiting liver transplantation.

Discussion

Our findings suggest that despite initial encouraging results with UDCA in PBC—as shown by improvement in symptoms of fatigue and pruritus and improvement in results of biochemical liver
tests—the disease can advance histologically to cirrhosis with the development of portal hypertension and esophageal variceal bleeding. In evaluating the efficacy of medical therapy for PBC, however, it must be emphasized that multiple aspects of the disease must be considered, including the effect on the following clinical parameters: (a) symptoms, (b) biochemical liver tests; (c) histological progression of disease, (d) time to development of complications of portal hypertension, and (e) time to development of liver failure. To date, UDCA therapy has been shown to be associated with early improvement of pruritus and fatigue and with improvement in biochemical liver test results. However, the data are conflicting or nonexistent with regard to the effect of UDCA therapy on preventing histological progression of the disease, in preventing the development of portal hypertension and its complications, and on prolonging survival. Furthermore, in most studies reported to date, follow-up has been less than 2 years.

In summary, our findings suggest that in PBC patients treated with UDCA, improvement in symptoms and results of biochemical liver tests is not necessarily associated with halting histological progression to cirrhosis or the development of portal hypertension and its life-threatening complications. At the present time, several controlled UDCA trials in PBC are in progress to further address the issue of efficacy.

References

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