Ursodeoxycholic acid for treatment of cholestasis in patients with hepatic amyloidosis

Ursodeoksiholna kiselina za lečenje holestaze kod bolesnika sa amiloidozom jetre

Dominik Faust*, Bora Akoglu†, Gordana Ristic†, Vladan Milovic†

Asklepios Hospital, *Department of Medicine, Langen, Germany; MediClin Deister Weser Hospital, †Department of Gastroenterology and Oncology, Bad Muender, Germany

Abstract

Background. Amyloidosis represents a group of different diseases characterized by extracellular accumulation of pathologic fibrillar proteins in various tissues and organs. Severe amyloid deposition in the liver parenchyma has extrahepatic involvement predominantly in the kidney or heart. We evaluated the effect of ursodeoxycholic acid, in four patients with severe hepatic amyloidosis of different etiologies, who presented with increased alkaline phosphatase and γ-glutamyl transferase. Case report. The study included four patients who presented with amyloidosis-associated intrahepatic cholestasis. Three of them had renal amyloidosis which developed 1–3 years before cholestasis occurred, the remaining one having intrahepatic cholestasis as the primary sign of the disease. Amyloidosis was identified from liver biopsies in all patients by its specific binding to Congo red and green birefringence in polarized light. The biochemical nature and the class of amyloid deposits were identified immunohistochemically. In addition to their regular treatment, the patients received 750 mg ursodeoxycholic acid per day. After 2–4 weeks all patients had a significant decrease of serum alkaline phosphatase and γ-glutamyl transferase, and their general status significantly improved. Conclusion. Treatment with ursodeoxycholic acid may be beneficial in patients with hepatic amyloidosis, and do extend indications for the use of ursodeoxycholic acid in amyloidotic cholestatic liver disease.

Key words: amyloidosis; cholestasis; biopsy; immunohistochemistry; deoxycholic acid.

Introduction

Amyloidosis represents a group of different diseases characterized by extracellular accumulation of pathologic fibrillar proteins (called amyloid on the basis of special tinctorial and optical properties) in various tissues and organs. Systemic amyloidosis may present as predominantly renal disease. Severe amyloid deposition in the liver parenchyma has been described as much less common than renal amyloidosis, occurring in approximately 5% of patients with simultaneous renal involvement. In turn, the majority of patients with proven hepatic amyloidosis had extrahepatic...
involvement predominantly in the kidney (47%) or heart (42%)\(^2\). Regarding poor median survival rate of patients with severe hepatic amyloidosis and the failure of existing treatment options to improve survival and relieve cholestasis, novel therapeutic approaches are obviously needed.

When used to dissolve gallstones in patients with chronic active hepatitis, the dihydroxylated bile acid, urso-deoxycholic acid, improved both serum transaminases and chronic active hepatitis, the dihydroxylated bile acid, ursodeoxycholic acid has also been used in patients with cystic fibrosis, and is the treatment of choice in primary biliary cirrhosis\(^3,4,6\). In the present study, we administered ursodeoxycholic acid to four patients with cholestasis due to amyloidosis with hepatic involvement. Rapid improvement of cholestasis after the treatment was initiated, recurrence of cholestasis after ursodeoxycholic acid was temporarily discontinued and repeated improvement after the drug was reintroduced, suggest that ursodeoxycholic acid may be an efficient therapy in patients with cholestasis due to hepatic amyloidosis.

**Case report**

The study included four patients who presented with amyloidosis-associated intrahepatic cholestasis (Table 1). Three of the four patients had renal amyloidosis which developed 1–3 years before cholestasis occurred. The patient 1 was a 44-year-old Caucasian female with immunoglobulin-light-chain-\(\lambda\)-related (AL\(\lambda\)) amyloidosis, while two males, patient 2 (65-year-old Caucasian) and patient 3 (40-year-old African), had amyloid protein A (AA) amyloidosis. In contrast, the patient 4 (70-years-old Caucasian male) had no overt renal amyloidosis, and intrahepatic cholestasis was the primary sign of the disease. Familial Mediterranean fever was the cause of amyloidosis in one of two patients with AA amyloidosis (patient 2). In patients 1, 3 and 4 no cause could initially be identified, and, in particular, chronic inflammatory bowel disease and Mediterranean fever were ruled out.

Two out of four patients (patients 1 and 2) complained to pruritus as the only cholestasis-related symptom. Patients 1 and 2 were in the end-stage renal disease and undergoing hemodialysis. They were both receiving ACE inhibitors and calcium antagonists to treat renal hypertension. The patient 3 had moderately impaired renal function without indications for hemodialysis, and was receiving no medication. The patient 4 had coronary heart disease and, as regular therapy, was receiving acetylsalicylic acid and metoprolol daily.

Laboratory data are summarized in Tables 1 and 2. Extrahepatic cholestasis was excluded in all patients by ultrasound. Magnetic resonance cholangiopancreatography was additionally done in Patient 3, confirming normal morphology of intra- and extrahepatic bile ducts.

Liver biopsies were performed in all patients and evaluated separately by two pathologists. They revealed severe capillary amyloid deposits along the sinusoids and in the walls of hepatic arteries, and were diagnostic for amyloidosis, according to the criteria described before\(^7\). Amyloid was identified at light microscopy by its specific binding to Congo red and its green birefringence in polarized light. The biochemical nature and the class of amyloid deposits were identified immunohistochemically, as previously described\(^8\).

<table>
<thead>
<tr>
<th>Survey of blood cell count, clinical chemistry and clotting tests before and after four weeks of treatment with ursodeoxycholic acid (750 mg per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
</tr>
<tr>
<td><strong>Week 0</strong></td>
</tr>
<tr>
<td>Hemoglobin, (g/dL)</td>
</tr>
<tr>
<td>Creatinine, (mg/dL)</td>
</tr>
<tr>
<td>Cholesterol, (mg/dL)</td>
</tr>
<tr>
<td>Prothrombin time, (%)</td>
</tr>
</tbody>
</table>

**Table 1**

<table>
<thead>
<tr>
<th>Immunological markers of patients studied</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
</tr>
<tr>
<td><strong>ANA</strong></td>
</tr>
<tr>
<td><strong>AMA</strong></td>
</tr>
<tr>
<td><strong>ANCA</strong> (screen)</td>
</tr>
<tr>
<td><strong>IgG (g/dL)</strong></td>
</tr>
<tr>
<td><strong>IgA (mg/dL)</strong></td>
</tr>
<tr>
<td><strong>IgM (mg/dL)</strong></td>
</tr>
</tbody>
</table>

**Table 2**

Liver biopsies of all four patients revealed amyloid deposits which were positive to Congo red staining (Figure 1). Further molecular characterization of the type of amyloidosis showed that the patient 4 suffered from hereditary ApoAI-amyloidosis, a rare disorder characterized by a mutation in the gene for apolipoprotein AI.

Prior to the initiation of the treatment, informed consent was obtained from each patient and the study protocol (conforming to the ethical guidelines of the 1975 Declaration of Helsinki) was approved by the Ethics Committee of the Johann Wolfgang Goethe University School of Medicine in Frankfurt.

Independent from body weight, 750 mg ursodeoxycholic acid per day (Ursofalk, Dr Falk Pharma GmbH, Freiburg, Germany) divided into three daily doses were administered to all patients.

After 2 to 4 weeks of treatment, a significant decrease in serum alkaline phosphatase and gamma-glutamyl transferase levels in comparison to pretreatment values was observed in all patients, while other liver function tests remained unchanged (Figure 2). Patients 1 and 2 also reported a significant improvement of their pruritus. There was no change in the liver size on follow up (ultrasound) and renal function tests remained unchanged. Four weeks after the treatment with ursodeoxycholic acid was started the patients were discharged from our outpatients clinic and were treated by their general practitioners, with regular (1–3 months) follow-up visits to us. Three of the patients (patients 1–3), however, interrupted ursodeoxycholic acid treatment only a few weeks after being discharged, since their family physicians decided, due to high costs, not to prescribe the drug any longer. In the patient 4 alkaline phosphatase decreased to normal (100 U/L), and in patients 2 and 4 gamma-glutamyl transferase fell to one third of the pretreatment values.

The patients 1–3 were seen again in our clinic after ursodeoxycholic acid treatment was discontinued; in all three, cholesstatic parameters again markedly increased (Figure 2). Reintroducing ursodeoxycholic acid (750 mg per day) again resulted in a decrease in serum alkaline phosphatase and gamma-glutamyl transferase levels as early as one week after the treatment was reintroduced. Again, there was no change in other liver function tests.

Ursodeoxycholic acid was well tolerated by all patients. However, they all refused a repeated liver biopsy aimed to assess possible histological changes due to ursodeoxycholic acid treatment. One of the patients (patient 1) died of heart failure shortly after the treatment with ursodeoxycholic acid was reinitiated, but the other two maintained stabilised parameters of cholestasis over time (Figure 2). The patient 2

again interrupted ursodeoxycholic acid therapy after a treat-
ment period of six weeks; alkaline phosphatase and gamma- 
glutamyl transferase again increased, and returned to previ-
ous values after the treatment was reintroduced. The patient 
4 was taking ursodeoxycholic acid without any interruption 
for almost six months, and, on the last follow-up, had nearly 
normalized parameters of cholestasis (Figure 2).

Discussion

Here we describe four patients with hepatic amyloidosis 
and cholestasis, who were successfully treated with ursode-
oxoycholic acid and stabilized their laboratory parameters of 
cholestasis within weeks after the initiation of therapy. The 
effect of ursodeoxycholic acid was specific, since temporary 
discontinuation of the drug resulted in a recurrent increase in 
alkaline phosphatase and gamma-glutamyl transferase, which 
again returned to nearly normal values after ursodeoxycholic 
acid was reintroduced. Among our four patients, however, 
one patient died during the course of treatment due to heart 
failure caused by amyloidosis of the heart.

A relatively small series of patients with liver amyloi-
dosis available for this study at present does not allow any 
conclusion whether treatment with ursodeoxycholic acid can 
fluence survival. If any analogy between the two chole-
static diseases can be helpful, in patients with primary biliary 
cirrhosis it has been shown that ursodeoxycholic acid delays 
the need for transplantation, while the posttransplantation 
outcome of ursodeoxycholic acid-treated patients is not dif-
ficult from those who were administered placebo 10,11.

Chronic cholestatic liver diseases are characterized by 
impaired bile flow, caused by different mechanisms and cell 
structures, like the bile salt dependent and independent bile 
flow, different export pumps, ATP, glutathione and the cyto-
skeleton 12-14. Amyloidosis with liver involvement is rela-
tively rare in comparison to amyloidotic disease of the kid-
neys, lung and heart, is characterized by the accumulation of 
amyloid fibrils in the liver parenchyma and ultimately may 
result in chronic intrahepatic cholestasis 15. Amyloid is de-
posited in the parenchyma and in the wall of blood vessels in 
the liver, as well as around the bile canaliculi.

Experimental evidence suggests that, in principle, ur-
sodeoxycholic acid acts at least on two major levels in re-
lieving cholestasis in man: it protects cholangiocytes 
against cytotoxic effects of hydrophobic bile acids and bile 
acid-induced apoptosis, and it stimulates hepatobiliary se-
cretion 16. On cellular level, ursodeoxycholic acid stimu-
lates ATP secretion in the liver, mobilizes intracellular cal-
cium and activates phospholipase A, induces a pleiotropic 
metabolic response in the hepatocyte by activating protein 
kinase C, inserts bile acid transporters in the apical pole of 
the hepatocyte canalicular membrane, and stabilizes the 
hepatocyte membranes and liver mitochondria 17-23. In pa-
patients with biliary liver diseases it has also been suggested 
that ursodeoxycholic acid acts primarily within the bile ca-
nalicular lumen, by preventing disruption of the plasma 
membrane of bile duct epithelial cells by hydrophobic bile 
acids 24. Whether one or all of these mechanisms lie be-
nearth the described anti-cholestatic effect of ursodeoxy-
cholic acid in patients with severe liver amyloidosis, still 
remains to be seen.

Conclusion

Our data imply that ursodeoxycholic acid should be 
used to treat cholestasis in patients with liver amyloidosis. 
Further clinical studies at a larger patient group are obvi-
ously needed to assess this promising conclusion.

R E F E R E N C E S

1. Glenner GG. Amyloid deposits and amyloidosis: the beta-
1333–43.
2. Gertz MA, Kyle RA. Hepatic amyloidosis: clinical appraisal in 
3. Leuschner U, Leuschner M, Sieratzki J, Kurtz W, Hübner K. Gall-
stone dissolution with ursodeoxycholic acid in patients with 
chronic active hepatitis and two years follow-up. A pilot study. 
A, et al. Ursodeoxycholic acid in primary biliary cirrhosis: re-
sults of a controlled double-blind trial. Gastroenterology 1989; 
5. Ponpon RE, Lindor KD, Cauch-Dudek K, Dickson ER, Ponpon R, 
Huebste EJ. Combined analysis of randomized controlled tri-
als of ursodeoxycholic acid in primary biliary cirrhosis. Gastro-
enterology 1997; 113(3): 884–90.
6. Huebste EJ. Management of primary biliary cirrhosis. The American 
Association for the Study of Liver Diseases practice 
7. Sasaki M, Nakanuma Y, Terada T, Hoso M, Saito K, Hayashi M, 
et al. Amyloid deposition in intrahepatic large bile ducts and 
peribiliary glands in systemic amyloidosis. Hepatology 1990; 
8. Linke RP. Highly sensitive diagnosis of amyloid and various 
amyloid syndromes using Congo red fluorescence. Virchows 
9. Souar AK, Hawkins PN, Vigilance DM, Tennent GA, Booth SE, 
10. Lazaridis KN, Goris CJ, Lindor KD. Ursodeoxycholic acid 'mechanisms of action and clinical use in hepatobiliary disor-
11. Heathote EJ, Stone J, Cauch-Dudek K, Ponpon R, Chequiers O, 
Lindor KD, et al. Effect of pretreatment with ursodeoxycholic 
acid therapy on the outcome of liver transplantation in patients 
269–74.
12. Ponpon R, Chequiers O, Ponpon RE. Chronic cholestatic dis-
13. Tranner M, Meier PJ, Beyer JL. Molecular pathogenesis of chole-
14. Meier PJ. Molecular mechanisms of hepatic bile salt transport 
from sinusoidal blood into bile. Am J Physiol 1995; 269(6 Pt 
1): G801–12.


The paper received on October 3, 2008.