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Ursodeoxycholic acid for treatment of cholestasis in patients with hepatic amyloidosis

Ursodeoksiholna kiselina za lečenje holestaze kod bolesnika sa amiloidozom jetre

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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.

Apstrakt

Uvod. Amiloidoza predstavlja grupu različitih oboljenja koju karakteriše vanćelijsko nakupljanje patoloških fibrilnih proteina u različtim tkivima i organima. Značajno nakupljanje depozita u parenhimu jetre prati ekstrahepatična zahvaćenost pre svega bubrega ili srca. Ispitivan je efekat ursodeoksiholne kiseline kod četiri bolesnika sa amiloidozom jetre različite etiologije koji su primljeni zbog povišenja alkalne fosfataze i gama glutamil transferaze. **Prikaz bolesnika.** Opisali smo četiri bolesnika sa intrahepatičkom holestazom udruženom sa amiloidozom. Tri od četiri bolesnika imala su amioloidozu bubrega koja se razvila 1–3 godine pre pojave holestaze, a jedan bolesnik holestazu kao prvi znak bolesti. Amiloidoza je dokazana iz biopsija jetre nakon specifičnog bojenja Kongo crvenim. Biološka priroda i klasa amiloida ispitana je imunohistohemijski. Zajedno sa njihovom uobičajenom terapijom, bolesnici su lečeni ursodeoksiholnom kiselinom, 750 mg dnevno. Posle 2–4 nedelje kod svih bolesnika dokazan je značajni pad alkalne fosfataze i gama glutamil transferaze, i njihovo opšte stanje značajno se popravilo. **Zaključak.** Terapija ursodeoksiholnom kiselinom uspešna je kod bolesnika sa amiloidozom jetre, čime se proširuje indikacija za davanje ursodeoksiholne kiseline kod bolesnika sa holestazom koja nastaje kao posledica jetrene amiloidoze.

Ključne reči:
amiloidoza; holestaza; biopsija; imunohistohemija; dezoksiholna kiselina.

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 [1]. In turn, the majority of patients with proven hepatic amyloidosis had extrahepatic

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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 therapeutical approaches are obviously needed.

When used to dissolve gallstones in patients with chronic active hepatitis, the dihydroxylated bile acid, ursodeoxycholic acid, improved both serum transaminases and cholestasis-indicating enzymes [3]. Ursodeoxycholic acid has also been used in patients with cystic fibrosis, and is the treatment of choice in primary biliary cirrhosis [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-λ-related (ALλ) 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 1

Survey of blood cell count, clinical chemistry and clotting tests before and after four weeks of treatment with ursodeoxycholic acid (750 mg per day)

	Patient 1		Patient 2		Patient 3		Patient 4		Normal range
	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	
Hemoglobin, (g/dL)	10.2	10.6	11.5	11.3	13.4	13.8	13.8	12.1	12.5–17.5
Leucocytes, (nL)	8.3	9.2	7.6	10.8	6.45	5.60	8.78	8.11	3.5–9.8
Sodium, (mmoL/L)	141	140	142	137	136	141	138	143	135–155
Creatinine, (mg/dL)	5.9	8.0	6.8	6.8	2.9	2.7	0.80	1.1	< 1.44
Cholesterol, (mg/dL)	283	256	166	236	172	185	232	211	< 200
Albumin, (g/dL)	4.7	3.7	3.8	3.8	3.5	3.7	4.6	4.1	3.0–5.0
Bilirubin, (mg/dL)	0.4	1.2	0.8	0.9	0.4	0.4	0.5	0.6	< 1.1
Prothrombin time, (%)	70	73	68	70	82	83	91	86	70–100

Patient 1: 44-year-old Caucasian female with AL-lambda amyloidosis; patient 2: 65-year-old Caucasian male with AA amyloidosis and familial Mediterranean fever; patient 3: 40-year-old African male with AA amyloidosis but without clinical features of chronic inflammatory disease; patient 4: 70-years-old Caucasian male, with hereditary ApoAI-amyloidosis

Table 2

Immunological markers of patients studied

	Patient 1	Patient 2	Patient 3	Patient 4	Normal values
ANA	negative	negative	negative	negative	negative
AMA	negative	negative	negative	negative	negative
ANCA (screen)	negative	negative	negative	negative	negative
IgG (g/dL)	0.85	1.32	1.07	1.48	0.8–1.8
IgA (mg/dL)	0.22	0.35	0.29	0.31	0.1–0.45
IgM (mg/dL)	0.01	0.12	0.20	0.19	0.06–0.26

Patient 1: 44-year-old Caucasian female with AL-lambda amyloidosis; patient 2: 65-year-old Caucasian male with AA amyloidosis and familial Mediterranean fever; patient 3: 40-year-old African male with AA amyloidosis but without clinical features of chronic inflammatory disease. Patient 4: 70-years-old Caucasian male, with hereditary ApoAI-amyloidosis. ANA – antinuclar antibodies; AMA – antimitochondrial antibiodies; ANCA antineutrophil cytoplasmic antibodies; Ig – immunoglobulins

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 [9].

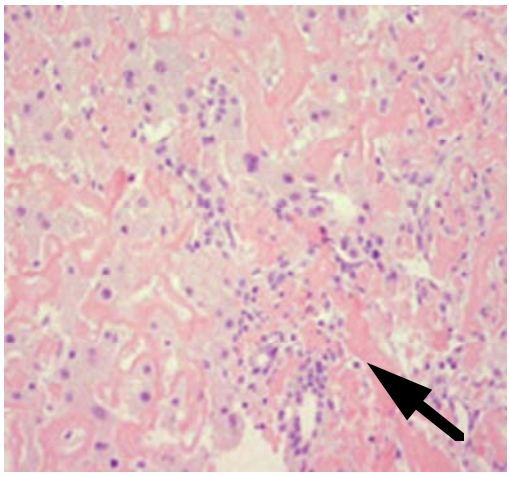

Fig. 1 – Liver biopsy of patient 3. The other two patients exhibited identical findings. In the vicinity of a portal tract, extensive extracellular amyloid deposits are seen in all sinusoids (arrow), with concomitant finding of atrophic hepatocytes (Congo red staining, magnification 400×).

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-glytamyl 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, cholestatic 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.

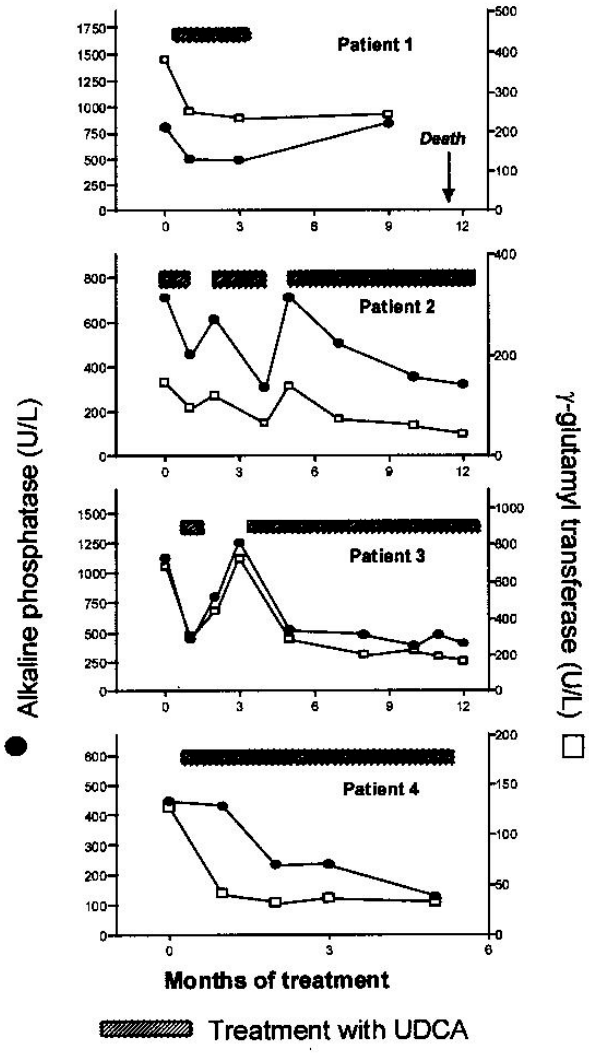

Fig. 2 – Decrease in serum alkaline phosphatase and gamma-glutamyl transferase during treatment with ursodeoxycholic acid (UDCA; 750 mg per day) and their reversal after the treatment was temporarily discontinued. Patient 1: 44-year-old Caucasian female with AL-lambda amyloidosis; patient 2: 65-year-old Caucasian male with AA amyloidosis and familial Mediterranean fever; patient 3: 40-year-old African male with AA amyloidosis but without clinical features of chronic inflammatory disease; patient 4: 70-years-old Caucasian male, with hereditary ApoAI-amyloidosis. (normal range: AP < 180 U/L, γ-GT < 28 U/L).

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 treatment period of six weeks; alkaline phosphatase and gamma-glutamyl transferase again increased, and returned to previous 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 amylodosis and cholestasis, who were successfully treated with ursodeoxycholic 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 amyloidosis available for this study at present does not allow any conclusion whether treatment with ursodeoxycholic acid can influence survival. If any analogy between the two cholestatic 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 different 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 cytoskeleton [12–14]. Amyloidosis with liver involvement is relatively rare in comparison to amyloidotic disease of the kidneys, lung and heart, is characterized by the accumulation of amyloid fibrilis in the liver parenchyma and ultimately may result in chronic intrahepatic cholestasis [15]. Amyloid is deposited 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, ursodeoxycholic acid acts at least on two major levels in relieving cholestasis in man: it protects cholangiocytes against cytotoxic effects of hydrophobic bile acids and bile acid–induced apoptosis, and it stimulates hepatobiliary secretion [16]. On cellular level, ursodeoxycholic acid stimulates ATP secretion in the liver, mobilizes intracellular calcium 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 patients with biliary liver diseases it has also been suggested that ursodeoxycholic acid acts primarily within the bile canalicular 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 beneath the described anti-cholestatic effect of ursodeoxycholic 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 obviously needed to assess this promising conclusion.

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