URSODEOXYCHOLIC ACID EFFECTS ON CYSTIC FIBROSIS LIVER DISEASE

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Abstract

Cystic fibrosis (CF) is the most frequent monogenic autosomal recessive disease with lethal potential, manifested by an important clinical polymorphism. Cystic fibrosis associated liver disease (CFLD) is the second non-pulmonary cause of death in children with cystic fibrosis, being an important monitoring problem. The only existent treatment is ursodeoxicholic acid (UDCA), which has controversial efficiency. The aim of this study was to evaluate the efficiency of the treatment with UDCA on CFLD evolution. The study included 51 patients with CFLD, prospectively monitored for five years. They were routinely followed-up by clinical assessment, liver biochemical tests and ultrasound examinations. All patients with CFLD received UDCA in a dose of 15-20 mg/kg bw/day permanently. Liver tests results and ultrasound Williams score were used for CFLD monitoring as primary endpoints. After UDCA administration, transaminases values decreased significantly in one year of treatment. Important improvements in liver parenchyma were documented by the ultrasound score. UDCA showed a valuable influence on CFLD outcome and should be recommended as soon as diagnosis is made.

Rezumat

Fibroza chistică (FC) este cea mai frecventă boala monogenică autozomal recesivă cu potenţial letal, manifestată printr-un polimorfism clinic important. Hepatopatia asociată fibrozei chistice (HFC) este a doua cauză non-pulmonară de deces la copiii cu fibroză chistică, fiind o complicaţie importantă a bolii. Singurul tratament existent este acidul ursodeoxicolic (AUDC), care are o eficienţă variabilă, fiind discutabilă din punct de vedere al medicinei bazate pe dovezi. Scopul acestui studiu este de a evalua eficienţa tratamentului cu acid ursodeoxicolic la pacienţii cu hepatopatie asociată fibrozei chistice. Studiul prospectiv a inclus 51 de pacienţi cu hepatopatie, urmăriţi pe o perioadă de cinci ani. Pacienţii au fost monitorizaţi din punct de vedere clinic, biochimic, iar evaluarea parenchimului hepatic s-a facut ecografic. Toţi pacienţii cu HFC au primit acid ursodeoxicolic în doză de 15-20 mg/kg corp/zi permanent. Rezultatele testelor hepatice şi scorul ecografic Williams au fost folosite pentru monitorizarea hepatopatiei sub tratamentul instituit. Cincizeci şi unu de pacienţi au fost diagnosticaţi cu HFC, însumând o prevalenţă de 32,27 %. După începerea administrării AUDC, valorile transaminazelor au scăzut în mod semnificativ într-un an de tratament. Îmbunătăţiri importante în textura hepatică au fost documentate prin scorul ecografic. AUDC a avut un efect benefic asupra evoluţiei HFC şi ar trebui să fie recomandat încă de la stabilirea diagnosticului de hepatopatie.

Keywords: cystic fibrosis liver disease (CFLD), ursodeoxycholic acid (UDCA), paediatrics

Introduction

Cystic fibrosis (CF) is the most frequent monogenic disease in Caucasian population [20], with autosomal recessive transmission and a significant fatal prospective [12]. The disease's incidence is about one in 2500-3000 of new-born [20], 1: 2054 in Romania [18], and a very important rate of carrier population of 1 in 25 people [1]. The genetic substrate consists in mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene that encrypts the activity of the chloride conductor protein [12, 19]. Patients with CFTR mutations have abnormal chloride conduction across the apical membrane of epithelial cells, resulting in thickened excretions in the liver, respiratory tract, pancreas, intestines, sweat glands, deferens vessels [20]. The clinical status of cystic fibrosis includes pulmonary obstructive disease, liver disease, steatorrhea, related diabetes, failure to thrive [19, 21]. Cystic fibrosis associated liver disease (CFLD) is the most important non-

pulmonary cause of death, being responsible of 2.5% of patients death [7]. CFLD pathogenesis is secondary to the CFTR protein defect in the cholangiocytes; the effect is an increased viscous secretion and subsequent biliary obstruction, leading to focal biliary cirrhosis and progressive periportal fibrosis [7, 11, 21]. The only therapeutic option is ursodeoxycholic acid (UDCA), which seems to have beneficial effect sustained by many studies [5, 22], although there are researchers who deny the role of UDCA in CFLD management [10]. UDCA is a hydrophilic biliary acid, non-toxic, used mainly for cholestatic diseases, with cytoprotective, antiapoptotic, choleretic and immunomodulatory properties [10, 16]. Mechanisms of UDCA action consist in direct cytoprotection on biological membranes, with a protective effect against apoptosis induced by endogenous bile acids and stimulation of bile secretion by hepatocytes and epithelial cells of the biliary ducts [17]. Recent data indicate that benefits of UDCA in CFLD may be related to the partial stimulation of the secretion of chloride channels calcium dependent and concomitant reduction of mucin secretion [6]. The optimal daily dose of UDCA recommended in CFLD is greater (20 mg/kg bw) than conventional doses used in other cholestatic liver diseases (10-15 mg/kg bw/day) due to poor intestinal absorption of bile acids in patients with cystic fibrosis [6]. Beneficial effects of ursodeoxycholic acid therapy on improving biochemical parameters [6], hysto-pathological aspects [2, 14], liver excretory function, bile drainage and essential fatty acid homeostasis were demonstrated by many studies [2, 6, 15]. Although there are not evidence-based data on clinical relevance and survival rate [12], UDCA is now widely used in the treatment of CFLD.

Materials and Methods

From 158 patients with CF, fifty one patients, diagnosed with CFLD according current guidelines [9], with the age between 4-18 years, were prospectively monitored from 2007 to June 2012. Patients were followed biannually in our National Cystic Fibrosis Centre Timisoara, Romania, after the diagnosis of cystic fibrosis. Patients or their parents accepted the inclusion in the study by

signing a written informed consent, in conformity with the Helsinki Declaration. Ethical Committee of the Clinical County Hospital approved the study developed in the National Cystic Fibrosis Centre of Timisoara, Romania. Physical evaluation, biochemical assessment, ultrasound examination and, in selected cases, magnetic nuclear resonance imaging (MRI), scintigraphy or transient elastography were completed. Cystic fibrosis associated liver disease (CFLD) was defined by the presence of at least two of the following features [7]:
1. hepatomegaly ± splenomegaly, clinically detected and confirmed by ultrasound;
2. persistent elevation of liver function test (more than 2 determination) and;
3. liver parenchyma alteration, detected on ultrasound examination, transient elastography or MRI, according to recent guidelines [9].

Biochemical liver investigations, including the assay of serum transaminases: aspartate amino-transferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), bilirubin, alkaline phosphatase, were performed in the Central Laboratory of Clinical County Hospital Timisoara. For CFLD diagnosis, only persistently increased values more than 1.5 IU/L of normal value, at three determinations [5, 9] were taken into consideration. Liver function was evaluated by the prothrombin time, international normalized ratio (INR) and albuminaemia. In order to avoid the interference of other aetiologies, viral or toxic hepatitis were excluded. Patients were evaluated every 6 months(for the first 2 years, afterwards once a year; visits being encoded as follows: T0 first visit, T1 after 6 months, T2 after 1 year, T3 after 2 years,T4 after 3 years , T5 after 4 years, T6 after 5 years. At the first visit (T0) we recommended the treatment with ursodeoxycholic acid 15-20 mg/kg bw/day.

Ultrasound examination was performed in the Paediatric II Department, using a 3.5-5 MHz convex probe with Doppler flow, at every programed visit. Ultrasound features were quantified according to the Williams score, [24] stating increased liver echogenicity, heterogeneity, nodularity, irregular margins; signs of portal hypertension [25]. Williams score was calculated using codification of changes according to Table I.

Table I

Williams scoring system

Score	1	2	3
Liver parenchyma	Homogeneity	Hyper-echogenicity	Heterogeneity
Liver edge	Smooth	-	Nodularity
Periportal fibrosis	Absent	Moderate	Severe

The ultrasound Williams score was used to quantify the liver features: score < 3 for normal liver, score between 3 and 4 as mild hepatopathy and score

between 5 and 8 suggesting moderate hepatopathy, while a score increased > 8-9 signifying multilobular liver cirrhosis.

In selected cases, with inconclusive ultrasound features other examinations like magnetic resonance (MRI) or transient elastography were performed. Transient elastography (TE) was used for measurement of liver stiffness by using FibroScan (Echosens, France) device in CFLD patients, through the intercostal space using a cut-off value of liver stiffness of 5 kPa [13].

For statistical processing IBM-SPSS v.18 was used. For the description of the continuous variables we used the mean and the standard deviation and for the description of ordinal and nominal variables we used frequency and percentage. ANOVA One way with post-hoc correction was used for comparison of transaminases in time; data were presented as median ± standard deviation. For relative share of different factors multifactorial analyse and multiple regression was applied.

Results and Discussion

Cystic fibrosis associated liver disease was diagnosed in 32.27 % of children with CF, with a median age at diagnosis of 13.94 ± 7.8 SD. The important prevalence of cystic fibrosis associated liver disease in our study was similar with data reported in literature [7, 8, 15], showed the importance of this complication in CF and the necessity for a correct treatment.

Evaluation of UDCA effect on transaminases
The transaminases increased values were considered a criterion for diagnosis of cystic fibrosis liver disease. At T0 - baseline, the values of transaminases were elevated, as follows: ALT (M 0 = 83.1 ± 29.75 IU/L, 95% confidence interval: 74.64-91.56) and AST (M 0 = 74.06 IU/K) in an important percentage of 82.35% patients. After one year of treatment, a decrease of transaminases by about 50% was registered, reaching an average normal value for both enzymes after the first year of

treatment (p = 0.003, with α = 0.01 coefficient) (Figure 1).

The results showed that after one year there was a significant decrease of transaminases values; ALT values decreased statistically significant from diagnosis to 6 months, 1 year, 2 years (p = 0.000) and subsequent values remained close to normal until the last year of study when a slight increase of 20% of their average (α = 0.001) was registered. AST decreased significantly from diagnosis to 6 months and 1 year (p = 0.000) and not statistically significant from 1 year to 2 years (p = 0.003), with the same ascendant trend in the last year, as ALT.

During the final evaluation in the fifth year (T6), AST seemed to have a tendency to decrease, while ALT values tended to increase.
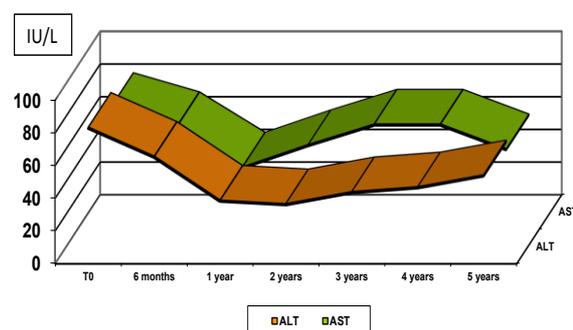

Figure 1.
Dynamics of ALT and AST activities in the CFLD patients

Therapeutic efficacy of UDCA in our study was found to have the maximum effect in the first two years of treatment. It seems that the effect of UDCA occurs in the first year of treatment, after this period the effect on transaminases is minimal. A subsequent increase of transaminases level, unaccompanied by clinical or ultrasound worsening of the disease state could be interpreted in the context of other factors influence, probably the use of other medication [23], hepatosteatosis [19], environmental factors, or unknown.

Table II

Serum levels of biochemical liver tests

Parameter	Value T0	Value T1	Value T2	Value T3	Value T4	Value T5	Value T6	Normal values
ALT (UI/L)	83.10 ± 29.75	65.30 ± 24.7	38.38 ± 18.45	36.22 ± 17.55	43.56 ± 12.34	46.55 ± 16.71	53.88 ± 20.73	< 45
AST (UI/L)	74.06 ± 28.252	62.38 ± 22.23	37.58 ± 17.48	34.46 ± 14.28	51.32 ± 17.6	63.86 ± 19.88	48.75 ± 15.9	< 40
Bilirubin (mg/dL)	1.07 ± 0.37	0.93 ± 0.51	1.02 ± 0.44	0.98 ± 0.57	1.06 ± 0.52	0.88 ± 0.48	0.98 ± 0.46	0.2 - 1
GGT (UI/L)	26.8 ± 8.73	35.1 ± 10.06	38.6 ± 11.2	47.87 ± 23.72	51.2 ± 25.7	48.3 ± 18.64	36.3 ± 17.45	< 35 Female < 70 Male
ALP (UI/L)	718.8 ± 433.7	727.5 ± 394.68	625 ± 455.7	567.6 ± 348.61	445.8 ± 225.83	327 ± 188.45	413.6 ± 274.63	< 350 < 650
Albumin (g/L)	45.5 ± 5.43	46.2 ± 7.88	44.9 ± 6.12	43.4 ± 4.43	41.7 ± 4.21	40.8 ± 2.87	41.8 ± 3.44	40-50
INR	0.9 ± 0.21	1.1 ± 0.25	0.98 ± 0.25	1.06 ± 0.32	1.1 ± 0.28	1.14 ± 0.38	1.18 ± 0.41	0.8-1.2

ALT = alanine transaminase/aminotransferase, AST = aspartate transaminase/aminotransferase, GGT = gamma-glutamyl transpeptidase, ALP = alkaline phosphatase, INR = international normalized ratio

Regarding the liver function evaluation, albuminaemia, prothrombin time TP, prothrombin index INR, were normal in the majority of patients.

It appears that, in terms of progress, the biochemical function tests, both, albumin and prothrombin index, showed constant values, with

normal hepatic function in most patients. In the normal range were maintained bilirubin and GGT, with few exceptions (Table II).

Hypoalbuminemia and prolonged INR were recorded in 2 patients with liver cirrhosis, who unfortunately, died.

Evolution of hepatic ultrasound features

Quantification of liver lesions was performed using the Williams score, based on the change of liver parenchyma, liver nodularity and periportal echogenicity [26].

Outcomes at baseline showed that majority of patients, 62.74% (32 patients), had a score between 4 and 6, significant for moderate CFLD; while mild CFLD, expressed as diffuse localized steatosis was found in 27.4% of our patients. A percent of 9.8% of patients had an ultrasound score > 9, significant for severe liver changes, with fibrosis, heterogeneous parenchyma, hyperechoic areas, cirrhotic nodules and nodular liver edge (Figure 2).
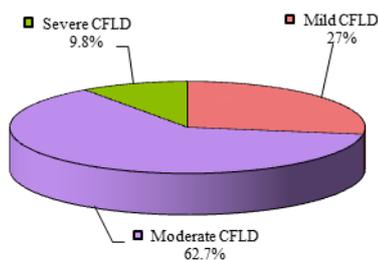

Figure 2.
CFLD forms distribution at the beginning of the study

UDCA treatment was instituted as previously described and ultrasound examinations were performed biannually. Because the ultrasound features do not change rapidly, the results regarding ultrasound forms were assessed at the beginning and at the end of the study (after 5 years).

After five years of treatment the results showed an increase of mild forms percentage from 27% to 35% (Figure 3), liver ultrasound texture improved in 6 patients. Only in two patients, Williams score increased, so the percent of severe CFLD augmented to 14%. Regarding the ultrasound features, the majority of our patients had a medium / light CFLD at the beginning of the study and the evolution was favourable, under UDCA treatment. The ultrasound scores had a good correlation with liver stiffness scores determined by elastography, with a median value of was 8.96 kPa ± 5.83 SD.

Even those with Williams score characteristic for multilobular cirrhosis, had a favourable outcome, with stagnation or slow progress of the lesions. No major decrease of Williams score was registered, but it is noteworthy that, in five years, the ultrasound score was stationary. It is possible that one of UDCA effects to be manifested in this regard, having a role in maintaining control on the development of lesions. In our group of patients we did not recorded any side effects.
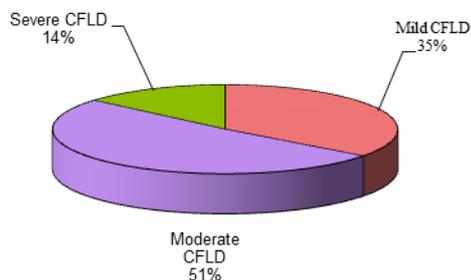

Figure 3.
CFLD forms distribution at the end of the study

Conclusions

Overall UDCA administration had a beneficial effect in our study, on both liver biochemical parameters and ultrasound liver changes. The effect consisted in decreasing of transaminases serum levels, in the first two years of treatment, with subsequent stationary evolution. Regarding the influence of ursodeoxycholic acid on the liver texture, the ultrasound score remained relatively constant during our study; but in severe liver disease cases, it did not have any impact. UDCA was a safe treatment option for our paediatric patients with liver disease associated to cystic fibrosis.

New studies are needed to determine its positive effect on the progress of disease in terms of survival.

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