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Ursodeoxycholic acid therapy in intrahepatic cholestasis of pregnancy: Results in real-world conditions and factors predictive of response to treatment

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ABSTRACT

Background: Ursodeoxycholic acid (UDCA) therapy is commonly used in intrahepatic cholestasis of pregnancy (ICP).
Aim: To evaluate the efficacy and tolerance of UDCA in real-world conditions and to search for factors predictive of response to treatment.
Methods: This observational study included 98 consecutive patients suffering from pruritus during pregnancy associated with increased ALT levels or total bile acid (TBA) concentrations, without other causes of cholestasis. The entire ABCB4 gene coding sequence was analyzed by DNA sequencing.
Results: UDCA was prescribed until delivery in all patients (mean dose 14.0 mg/kg/day; mean duration 30.4 days). Pruritus improved in 75/98 (76.5%) patients, and totally disappeared before delivery in 25/98 (25.5%). After 2–3 weeks of treatment, ALT levels decreased by more than 50% of base line in 67/86 (77.9%) patients and normalized in 34/86 (39.5%), and TBA concentrations decreased in 28/81 (34.6%). Only one patient stopped the treatment before delivery. On multivariate analysis, ALT >175 IU/l before treatment was associated with improvement of pruritus (OR 2.97, 95% CI 1.12–7.89, P = 0.029) and with decreased ALT (OR 18.61, 95% CI 3.94–87.99, P = 0.0002). ABCB4 gene mutation was not associated with response to treatment.
Conclusion: This study supports the use of UDCA as first line therapy in ICP.
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1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder which usually manifests during the second or third trimester of pregnancy, and then spontaneously improves after delivery [1]. ICP is characterized by generalized pruritus associated with an increase in serum aminotransferase activity and/or in serum bile acid concentration [2]. Pruritus may engender considerable discomfort, and the potential risks for pregnancy include premature delivery or sudden intrauterine fetal death (IUFD) [1,3]. ICP is a complex disease associated with hormonal and genetic factors [4,5]. Mutations in various genes encoding canalicular transporters have been found in patients with ICP, especially mutations in the ABCB4 (adenosine triphosphate-binding cassette, sub family B, member 4) gene encoding the canalicular transporter MDR3 [6,7]. The medical treatment of ICP is currently mainly based on ursodeoxycholic acid (UDCA) [8–10]. Based on a meta-analysis of nine randomized controlled trials (RCTs), and on the results of two recent RCTs not included in the metaanalysis, UDCA significantly reduces pruritus, and the levels of serum alanine aminotransferase activity and of bile acid concentration in patients suffering from ICP [11–13]. However data on the efficacy and tolerance of UDCA in real-world conditions are limited, and factors predictive of response to treatment with UDCA are unknown.

The aim of this study was to evaluate the efficacy and tolerance of UDCA in a real-world setting, and to search for factors predictive of response to treatment.

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2. Patients and methods

2.1. Design of the study

This was a single-center non-interventional study. All medical records of patients referred for hepatology consultation at the University Hospital Center of Tours (France) for liver disease during pregnancy and treated with UDCA between January 1999 and December 2013 were reviewed. All women were followed jointly by a single Hepatologist and the obstetric teams of several public or private hospitals. The patients were systematically examined after delivery for clinical evaluation and to check the results of liver function tests (LFTs). Patients with persistent abnormal LFTs were monitored in the longer term. The present study was approved by the Ethics Committee in Human Research of Tours, France (number 2014 027).

2.2. Inclusion and exclusion criteria

The criteria for inclusion in the analysis were: (1) occurrence of generalized pruritus during the current pregnancy, (2) fasting serum total bile acid (TBA) concentrations >10 μmol/l or alanine aminotransferase (ALT) levels >35 IU/l on at least two samples, (3) treatment by ursodeoxycholic acid, and (4) absence of intercurrent liver disease. The criteria for exclusion were: specific dermatosis of pregnancy, intercurrent acute or chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, benign recurrent intrahepatic cholestasis, intercurrent drug-induced liver injury, sepsis at diagnosis, treatment with UDCA before pregnancy, or loss to follow-up after delivery.

2.3. Data collection

The information researched in the medical records of the patients included: (1) past history, especially cholestasis during pregnancy, (2) characteristics of the current pregnancy, (3) evaluation of pruritus under UDCA therapy, (4) results of LFTs (see below), prothrombin time, serologic markers of viral hepatitis A, B, and C, and of cytomegalovirus and Epstein Barr Virus infections, and serologic markers of autoimmunity, (5) results of ultrasonography of liver and bile ducts, (6) modalities of treatment with UDCA, and other medications, (7) modalities of delivery, (8) characteristics of the newborn (birth weight, Apgar score at 5 min), and (9) maternal evolution after delivery. Whenever patients had been treated with UDCA for several episodes of ICP, only the first episode of ICP treated by UDCA was taken into account in the analysis.

2.4. Liver function tests

LFTs were measured in fasting state and included routine LFTs i.e., ALT, aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), and total and conjugated bilirubin, and the determination of serum TBA concentrations by an enzymatic method (Enzabile NYCOMED AS, Oslo, or Biostat diagnosis system, Cheshire) when available. LFTs were performed before the initiation of treatment with UDCA, regularly (usually once a week) under UDCA therapy until delivery, and after delivery. The results of LFTs are given at 37 °C. According to the references used by our laboratory for non-pregnant women, the following values were considered as upper normal limits: 35 IU/l for ALT, 30 IU/l for AST, 120 IU/l for AP, 35 IU/l for GGT, 17 μmol/l for total bilirubin, and 10 μmol/l for TBA. The cut-offs for ALT and TBA were chosen according these values and our experience in pregnant women [14]. For TBA, most studies in ICP use a cut-off between 6 and 10 μmol/l in fasted women [9], and we chose the cut-off of 10 μmol/l for greatest specificity. Severe ICP was defined as TBA concentrations >40 μmol/l [15,16].

2.5. Detection of genomic variants of the ABCB4 gene

Mutations in the ABCB4 gene were investigated in all patients after obtaining their informed written consent. DNA was extracted from peripheral venous blood leukocytes by standard procedures. The search for genomic variants of ABCB4 was conducted by direct sequencing in all 27 coding exons of the ABCB4 gene, as already published [7].

2.6. Evaluation of the efficacy of UDCA on pruritus

The patients were divided into three groups according to the evolution of pruritus under treatment with UDCA: (1) disappearance of pruritus before delivery (whatever the time and definitively), (2) improvement of pruritus (with or without disappearance) before delivery, and (3) lack of improvement of pruritus before delivery. The evaluation was made by the patient without the use of a visual analog scale. The concomitant administration of hydroxyzine was recorded but was not taken into account in this assessment.

2.7. Evaluation of the efficacy of UDCA according to liver function tests

The changes in LFT results between the onset of treatment with UDCA and delivery were studied, with special emphasis on the changes during the first three weeks of treatment.

2.8. Search for factors predictive of response to UDCA

The three independent judgment criteria used to search for factors predictive of response to treatment were: (1) improvement of pruritus (with or without disappearance) before delivery, (2) decrease in serum ALT levels (more than 50% of baseline) after two or three weeks of treatment, (3) decrease in serum TBA concentrations (more than 50% of baseline) after two or three weeks of treatment. Patients with missing data after two and three weeks of treatment were not included in this analysis.

The following explanatory variables were assessed to search for factors predictive of response to UDCA: prior history of pruritus or cholestasis during pregnancy, parity, multiple pregnancy, presence of ABCB4 gene mutation, biliary lithiasis (history of cholecystectomy or presence of gallstones on ultrasonography), ALT levels, GGT levels, total bilirubin levels, TBA concentrations, period between onset of pruritus and initiation of UDCA, and dosage of UDCA.

2.9. Statistical analysis

Descriptive values are expressed as means with standard deviation (SD) or 95% confidence intervals (CI). Proportions are expressed as percentages. Comparison of proportions between groups was performed with a Chi-2 test or exact Fisher's test. Comparison of means between groups was performed with Student's *t*-test, and ANOVA or Kruskal–Wallis tests according the number of patients. The explanatory variables which could influence the judgment criteria (improvement of pruritus, decrease in serum ALT levels, and decrease in serum TBA concentrations) were tested in successive models of univariate logistic regression, and variables with a P value lower than or equal to 0.25 were introduced in a multivariate model. Multivariate analysis followed the procedure of Hosmer and Lemeshow which consists of successively eliminating the less significant variables, one by one, and keeping only independent significant variables ($P < 0.05$) at the end. The results of the univariate

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