Ursodeoxycholic Acid Attenuates Hepatotoxicity of Multidrug Treatment of Mycobacterial Infections: A Prospective Pilot Study

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Abstract

Background: Tuberculosis (TB) remains a global health problem. The application of rifampicin-based regimens for antimycobacterial therapy is hampered by its marked hepatotoxicity which results in poor adherence and may contribute to prolonged therapy or treatment failure. The purpose of this prospective investigation was to evaluate the hepatoprotective effectiveness of oral ursodeoxycholic acid (UDCA) (250–500 mg TID) administered to TB- or non-TB mycobacterial (NTM)-infected patients with drug-induced hepatotoxicity and ongoing therapy. Methods: Study population: During 2009–2017, 27 patients (11 women, 16 men, aged 19–90 years; median age 44 years, 16 Caucasians, 10 Africans, 1 Asian) out of 285 patients with active TB (24/261) or NTM infections (3/24) treated at our TB Center developed clinically relevant hepatotoxicity. Oral UDCA was administered to treat hepatotoxicity. Results: Twenty-one out of 27 patients (77.8%) showed normalization of elevated enzymes (alanine transferase and aspartate aminotransferase), alkaline phosphatase, and bilirubin while continuing TB treatment and 5 patients demonstrated a significant reduction of liver enzymes (18.5%). No change was observed in 1 patient (3.7%). Drug dose was not reduced in all patients; they all showed radiological and clinical improvement. There were no significant side effects. Conclusion: Oral administration of UDCA to TB patients developing anti-TB drug-induced liver injury may reverse hepatotoxicity in adults.

Keywords: Drug-induced liver injury, tuberculosis, ursodeoxycholic acid

Introduction

Tuberculosis (TB) remains a major global health problem despite the availability of effective treatment. The currently recommended standard regimen for active TB is isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) for 2 months, followed by 4 months of isoniazid and rifampicin (6HR2ZE). Treatment with the properly implemented 6HR2ZE regimen has a success rate exceeding 95%. It prevents relapse and the emergence of multidrug-resistant strains.[1] The treatment of pulmonary nonmycobacterial infections is also based on multidrug regimens including rifampicin and clarithromycin.

Hepatotoxicity secondary to anti-TB therapy is reported in 2%–28% of patients.[2] This high variation is due to the different characteristics of the study cohorts, drugs involved, thresholds used to define liver damage, and the intervals of laboratory monitoring.

Except for ethambutol, all first-line anti-TB drugs as well as clarithromycin have the potential to cause hepatotoxicity. The spectrum of manifestations of anti-TB-induced hepatotoxicity ranges from asymptomatic elevations in liver enzymes to rare acute liver failure, leading rapidly to death or the need for liver transplantation.

TB treatment-related adverse events, including hepatotoxicity, account for significant morbidity leading to reduced effectiveness of therapy or to drug discontinuation. The

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Lang, et al.: UDCA attenuates TB drug-induced hepatotoxicity

Carefully designed experimental studies, although [15,16] Moreover, UDCA is frequently used in Japan for [16,18] The diagnosis of pulmonary NTM [1] The table [17] [14] [8‑13] developed drug-induced liver injury while on treatment for active TB. All treatment decisions were based on common medical standards only. Oral UDCA was administered to these patients at initial doses from 250 mg TID to 500 mg TID. None of the patients had cholangitis, cholecystitis, or pancreatitis. UDCA dose was reduced to 250 or 500 mg OD and finally withdrawn when the patients’ liver enzymes returned toward normal.

Ethics
The investigations were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (SRH WKG 35). Informed consent to analyze and publish the data in anonymous form was obtained from all patients. They all consented to the off-label use of UDCA.

Study population
The 24 patients with active TB and the 3 patients with pulmonary NTM disease had normal ALT and bilirubin/AP values before the initiation of treatment. None of these patients had coinfection with HIV, hepatitis B or C, preexisting overt liver disease, current high alcohol intake, renal failure, or received drugs affecting liver function tests.

Definition of anti-TB drug included hepatotoxicity and injury patterns.

Hepatotoxicity was defined as a treatment-emergent increase in (a) serum alanine aminotransaminase (ALT) greater than three (with symptoms) or five times (without symptoms) the ULN and (b) an increase of AP >2 ULN and/or bilirubin >2 ULN.

Three biochemical patterns of injury were classified: hepatocellular, cholestatic, and mixed hepatocellular/cholestatic. These assignments refer to histologic features of injury but are usually defined based on the patterns of serum liver enzyme elevations. Hepatocellular injury can be suggested by markedly elevated serum ALT and AST levels, while the AP, gamma-glutamyl transpeptidase (GGT), and/or bilirubin are normal or only modestly increased. An “R” ratio of ALT to AP of 5 or more was used to define a hepatocellular pattern of injury. In cholestatic drug-induced liver injury, serum AP, GGT, and bilirubin are predominantly elevated with an R ratio of ALT to AP levels of minimally 2 or less. In cases of mixed injury, with similar elevations in serum ALT and AP, an R ratio of ALT to AP between 2 and 5 was used. Liver biopsies performed in five patients with anti-TB drug-induced liver injury showed intrahepatic cholestasis.

Monitoring of liver function tests.
Liver function tests were performed during the 1st week on multidrug therapy at least twice weekly and as needed.

Measurements of hematologic parameters and renal function were done to document safety of UDCA.

Results
The study population encompassed a wide age range (19–90 years); most of the patients were men, born in Germany,

management of patients is complicated by the need to interrupt treatment and rechallenge with the standard drugs, as liver injury may be transient in many cases. The occurrence of anti-TB drug-induced liver injury is unpredictable, although risk factors have been identified. However, the effectiveness of hepatoprotective drugs is not well defined.[4‑7]

Ursodeoxycholic acid (UDCA), a naturally occurring hydrophilic bile acid, has been used mostly off-label for the treatment of a variety of acute and chronic liver diseases, including primary biliary cirrhosis (licensed drug), primary sclerosing cholangitis, cystic fibrosis-related liver disease, pregnancy-induced intrahepatic cholestasis, and drug-induced liver injury.[8‑13] Carefully designed experimental studies suggest a protective effect of UDCA pretreatment on isoniazid plus rifampicin-induced liver injury in mice.[14] Clinical data, however, are rare, and the effects of UDCA on anti-TB drug-induced hepatotoxicity are not clear.[15,16] Recently, Russian authors published a small randomized study using UDCA in children with TB and drug-induced hepatotoxicity. They found a relevant hepatoprotective effect of UDCA.[17] Moreover, UDCA is frequently used in Japan for isoniazid-induced acute liver injury in adult patients with TB infection. The anecdotal data are inconsistent.[16,18]

We conducted a prospective pilot study to assess the hepatoprotective effectiveness of oral UDCA to attenuate liver injury induced by standard TB therapy.

Methods
A total of 285 adult patients (age over 18 years) were diagnosed and treated for active TB (n = 261) or pulmonary non-TB mycobacterial (NTM) infections (n = 24) at the TB center of the SRH Wald–Klinikum Gera between 2009 and 2017. All patients with newly diagnosed TB disease received the standard 6HR2ZE regimen; the drugs were dosed according to the German TB guideline for adults.[11] The diagnosis of pulmonary NTM infections was made by repeated isolation and identification of pathogens in the patients’ lungs with compatible clinical and radiological (computed tomography scan) features.

Thirty-nine out of 285 patients (incidence 13.6%) developed clinically relevant abnormal liver function tests during treatment (>2 upper limit of normal [ULN] of alkaline phosphatase [AP], bilirubin or >5 ULN alanine transferase [ALT]). Twelve patients with active TB were excluded from the analysis: four patients had preexisting chronic hepatitis or liver cirrhosis, one patient each suffered from malnutrition or advanced chronic kidney disease (Stage IV), one patient experienced intolerability of first-line anti-TB drugs (other than hepatotoxicity), and five patients had received other potentially hepatoprotective drugs (N-acetyl-L-cysteine, corticosteroids).

Study design
We performed a prospective pilot study of patients who developed drug-induced liver injury while on treatment for active TB. All treatment decisions were based on common medical standards only. Oral UDCA was administered to these patients at initial doses from 250 mg TID to 500 mg TID. None of the patients had cholangitis, cholecystitis, or pancreatitis. UDCA dose was reduced to 250 or 500 mg OD and finally withdrawn when the patients’ liver enzymes returned toward normal.
and had active TB of the lungs. Nonmycobacterial pulmonary infections were caused by M avium or intracellulare [Table 1].

**Course of liver injury**

Most patients (22 out of 27 patients) showed biochemical patterns of cholestatic liver disease (AP 2–4 ULN) and/or bilirubin 2–3 ULN within 1 to 2 weeks after starting anti-TB therapy. Patients with a biochemical pattern of hepatocellular liver injury had ALT levels of 5–6 ULN. None of the patients complained at the diagnosis of anti-TB liver injury of jaundice, abdominal pain, ascites, and signs of encephalopathy or showed abnormal coagulation tests.

In most of the patients, oral administration of UDCA was associated with a rapid decline (within 1 to 2 weeks) of elevated enzymes or bilirubin (normalization in 21 out of 27 patients, significant reduction in 5 patients). No measurable effect was seen in 1 patient. However, the enzymes of this patient did not further increase.

By comparison, all 12 TB patients excluded from the UDCA investigations showed no reduction in the biochemical parameters of liver injury, and the majority even progressed.

The hepatoprotective effect of UDCA in patients with anti-TB-induced liver injury occurred independently of age, gender, ethnicity, and type of mycobacterial infection.

**Outcome**

Hepatoprotection was effective in 96.3% of patients [Figure 1]. Anti-TB drug dosage was neither reduced nor discontinued in any of the patients. They all showed radiological and clinical improvement of active TB or pulmonary nonmycobacterial infection.

There were no adverse clinical, biochemical, or hematologic side effects of UDCA.

**DISCUSSION**

The main results of this prospective pilot study indicate that oral UDCA administered to patients with anti-TB therapy-induced liver injury may ameliorate elevated transaminases, AP, and bilirubin in most of these patients independently of patient characteristics or type of mycobacterial infection.

Transient mild changes in alanine transaminase and/or bilirubin are relatively common during antituberculous chemotherapy and do not allow to predict the further course or severity of hepatotoxicity.

Therefore, there is no unanimous recommendation for the cutoff level of liver dysfunction necessitating modification of treatment (dose reduction, discontinuation, and exchange of certain drugs). Undoubtedly, ALT levels five times or above that of normal or greater 2 or 3 fold levels of AP or bilirubin – as in our patients – are usually not spontaneously reversible.

Moreover, none of the TB patients with liver injury excluded from the investigations showed spontaneous normalization of liver injury parameters without UDCA. Most of these patients needed a discontinuation or change of regimen of TB therapy.

UDCA has been shown to exert anticholestatic effects in various cholestatic disorders and may be safely used long term in patients with cystic fibrosis, with very few side effects. Numerous potential mechanisms and sites of actions of UDCA have been unraveled in clinical and experimental studies. The relative contribution of these mechanisms to the anticholestatic action of UDCA may depend on the type and stage of cholestatic injury. Protection of injured cholangiocytes against the toxic effects of bile acids and the stimulation of impaired hepatocellular secretion by mainly posttranscriptional mechanisms seem to be relevant in cholestasis. 

Stimulation of impaired hepatocellular secretion and increases in bile flow could be crucial for improvement of serum liver function tests, as it is in some forms of drug-induced

**Table 1: Demographic characteristics of the study population**

| Parameter                              | Number  |
|----------------------------------------|---------|
| Number of patients (n)                 | 27      |
| Age, median (range)                    | 44 (19-90) |
| Gender (female/male)                   | 11/16   |
| Nationality                           |         |
| German                                 | 16      |
| African (Eritrea/Somalia)              | 10      |
| Asian (Afghan)                         | 1       |
| Site of infection                      |         |
| Lung                                   | 21      |
| Pleural                                | 2       |
| Lymph nodes                            | 1       |
| Larynx                                 | 1       |
| Gastrointestinal                       | 1       |
| Anti-TB drugs (hepatotoxic)            |         |
| Rifampicin                             | 27      |
| Isoniazid                              | 24      |
| Pyrazinamide                           | 24      |

TB: Tuberculosis

**Figure 1: Outcome of liver injury after treatment with ursodeoxycholic acid**
cholestasis. Inhibition of bile acid-induced hepatocyte apoptosis can have a role in cholestasis.

Our investigation may have limitations due to the small number and characteristics of the study population and the nonrandomized design of the study. However, the vast majority of our patients had reversed from progressive liver injury with UDCA treatment and could continue anti-TB treatment without dose reduction. They experienced no known side effects, but some complained of a bile taste sensation while on high doses. Abdominal discomfort was reported frequently with ingestion of the antituberculous drugs and additional effects of UDCA could not be discerned.

A positive effect of UDCA has been described also in Russian pediatric TB patients with anti-TB-induced liver injury, as published recently in Russian.[17] The authors had performed a randomized trial (UDCA vs. silymarin) in 77 children (3–14 years) and observed a more rapid and more frequent normalization of elevated ALT ( >5 ULN) with UDCA compared to silymarin treatment.

CONCLUSIONS

Oral administration of UDCA to TB patients developing anti-TB drug-induced liver injury may reverse hepatotoxicity in adults. There is an urgent need to perform a large trial to confirm the preliminary findings of our pilot study.

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Conflicts of interest

There are no conflicts of interest.

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