

Anti-Tuberculosis Drug Induced Liver Injury and Ursodeoxycholic Acid

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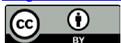
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Abstract

Hepatotoxicity induced by standard anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide) can result in significant morbidity and, rarely, even mortality. This major adverse side-effect of anti-tuberculosis treatment has a negative impact on patient adherence and patient outcomes as well as on tuberculosis control. Early recognition and prompt withdrawal of the offending drugs are the most critical interventions in the management of anti-tuberculosis drug-induced liver injury. No drug or herbal extract has been shown until recently to prevent or reverse anti-tuberculosis drug-induced hepatotoxicity. Ursodeoxycholic acid is the only FDA approved drug for the treatment of primary biliary cholangitis and has also been successfully used in various cholestatic liver diseases. Although still experimental, recent controlled clinical studies suggested that oral administration of ursodeoxycholic acid may prevent the onset of anti-tuberculosis drug-induced liver injury and accelerate the recovery of liver injury. These clinical data are supported by experimental models of anti-tuberculosis drug-induced hepatotoxicity. There is an urgent need for further randomized clinical trials to document the promising hepatoprotective properties of ursodeoxycholic acid.

Keywords

Ursodeoxycholic Acid, Hepatotoxicity, Rifampicin, Isoniazid, Pyrazinamide, Tuberculosis

1. Introduction

Hepatotoxicity is a frequent and potentially serious adverse effect of standard first line anti-tuberculosis drug (ATD) regimens containing the hepatotoxic compounds isoniazid, rifampicin, and pyrazinamide. There is a wide variety in the

reported incidence of ATD-induced liver injury in different studies (2% to 28%). This may be attributable to patient characteristics, the drug regimen involved, or the threshold of liver function tests used to define hepatotoxicity. The most widely used definitions of ATD-induced liver injury rely on serum alanine aminotransferase activities (ALT) (more than 5 times the upper limit of normal (ULN) and bilirubin concentrations (more than 2 times ULN without symptoms) or ALT levels more than 3 times ULN with clinical symptoms of hepatotoxicity [1] [2] [3].

The clinical presentations of ATD-induced liver injury vary from asymptomatic rises in serum transaminases, to acute hepatitis or even fatal liver failure. The high morbidity and mortality of ATD-induced severe liver injury may require interruption or modification of anti-tuberculosis treatment and reduce the efficacy of tuberculosis therapy. Discontinuation of first line drugs or nonadherence to treatment regimens may cause treatment failure, relapse and drug-resistance which can significantly reduce TB control [4] [5].

The pathogenesis underlying ATD-induced liver injury is poorly understood. Direct toxicity of the primary compound or its metabolites is the main cause but an immunologically mediated response may also play a role [6]. Once hepatotoxicity is diagnosed, all ATDs are temporarily withdrawn and sequential re-challenge of the involved drugs is used to identify the drug causing hepatotoxicity [7]. This can be a time-consuming effort for both patients and caregivers. No hepatoprotective agent has been proved beyond any doubt to be effective in ameliorating ATD-induced hepatotoxicity [8] [9] [10]. New therapies are needed to reduce the incidence and severity of ATD-induced hepatotoxicity.

Ursodeoxycholic acid (UDCA) has been successfully used for the treatment of primary biliary cholangitis and pregnant intrahepatic cholestasis [11]. Since UDCA has a favorable safety profile it seemed reasonable to treat cholestatic drug-induced liver injury (DILI) in a variety of diseases [12]. The usefulness of UDCA as a novel hepatoprotective agent for drug-induced hepatotoxicity was largely demonstrated by case reports and observational studies [13]-[21].

This narrative review describes the available experience with this drug in TB patients receiving standard first line treatment.

2. UDCA and ATD-Induced Liver Injury

UDCA is the major bile acid of the bile of black bears and has been used for centuries in traditional Chinese medicine as a remedy for cholestatic liver disease [22]. The therapeutic effects of UDCA for ATD-induced hepatotoxicity have been recognized but the data reported (case reports, case series,) are scarce and inconsistent [23] [24] [25].

We carried out a prospective pilot study to evaluate the hepatoprotective effectiveness of oral UDCA (250 - 500 mg, TID) administered to 27 adult patients with TB or non-mycobacterial infections and drug-induced liver injury (ALT levels > 5 - 6 ULN or bilirubin levels > 2 - 3 ULN) [26]. Despite continuation of standard first line anti-TB treatment, elevated enzymes ALT, AST, ALP and bi-

lirubin normalized in 78% of the patients and 19% of the patients showed a significant reduction in liver tests when UDCA was introduced. There was no significant change in liver enzymes/bilirubin in one patient. Due to the hepatoprotective effects there was no need to reduce drug dose in all patients. They all had radiological and clinical improvement, independent from age, sex, ethnicity, and severity of ATD-induced liver injury. In this series, there was no patient with fulminant hepatic failure. We concluded that oral administered UDCA to TB patients may reverse hepatotoxicity of first line anti-tuberculosis drugs.

Borzakova and Reyzis conducted a prospective randomized clinical trial to compare the effects of UDCA versus herbal extracts on the reversal of ATD-induced hepatotoxicity in Russia [27]. The study population included 77 young patients (children, adolescents) with pulmonary TB receiving standard anti-tuberculosis regimens. DILI was serious and ATD had to be stopped prior to randomisation. In group 1 39 patients were randomized to oral UDCA (20 mg/kg once, then 12 - 15 mg per day in 2 - 3 intakes). In group 2 38 children received herbal extracts (silymarin analogues or Hofetil) for ATD-induced hepatotoxicity. The results showed a more pronounced decrease in liver tests (aminotransferases, bilirubin) in the UDCA group compared to the group of patients receiving herbal extracts. The time to normalization of the liver tests was almost half in the UDCA group compared to the control group (29.6 days vs 49.6 days, $p > 0.05$). In patients continuing anti-TB therapy the increase in cholestatic parameters was significantly less in UDCA group than in the controls (14.7% vs 50.0%, $p < 0.05$).

Berestova *et al.* conducted two prospective randomized clinical trials to investigate prevention or reversal of ATD-induced hepatotoxicity in adult patients with pulmonary TB receiving the standard first line regimen. The patients were randomised to UDCA alone (250 mg twice per day), UDCA in combination with taurine, or to milk thistle extract.

Prophylactic administration of combined UDCA and taurine prevented the onset of anti-TB-induced DILI in most patients. Aminotransferase levels remained within the normal range in most patients, only 20% of the patients developed moderate and sometimes severe increases of serum liver transaminases. In contrast, most patients receiving prophylactic coadministration of milk thistle extract developed ATD-induced DILI and needed a modification of TB therapy (personal communication).

In a second randomized trial the authors examined the addition of UDCA alone or in combination with taurine to ongoing first-line TB treatment on anti-TB-DILI. The combination of UDCA and taurine resulted in normalisation of transaminases in most of these patients. UDCA alone was associated with a significant reduction in transaminases without complete normalization (Berestova, personal communication).

Carefully designed experimental investigations corroborate the findings of these clinical studies. Chen and co-workers examined the protective effects of UDCA on isoniazid plus rifampicin induced liver injury in mice [28]. The animals were

orally administered UDCA 30 minutes before isoniazid and rifampicin. UDCA pre-treatment significantly alleviated hepatic apoptosis. The UDCA-mediated protective effects seemed to be associated with its antioxidative and anti-apoptotic effects.

UDCA was well tolerated. None of these prospective clinical studies reported any relevant adverse effects of mid-to long-term UDCA therapy in humans.

3. Mechanisms of Action of UDCA

The specific mechanisms underlying the protective effect of UDCA on anti-TB-DILI are unknown.

UDCA acts on the liver through a variety of complex and complementary mechanisms. The main effects are: 1) protection of hepatocytes against bile-acid induced apoptosis 2) protection of cholangiocytes against cytotoxicity of hydrophobic bile acids 3) stimulation of hepatobiliary secretion of bile acids, 4) suppression of immune responses, and 5) anti-inflammatory effects [12] [28].

Perspective of UDCA in TB treatment

UDCA is an inexpensive and well tolerated medication that has shown the potential to alleviate DILI from standard TB regimens in a small number of prospective studies. In most TB patients raised liver functions tests entail a stop and rechallenge strategy which can be a burden for patients and their treating physicians. Prevention of hepatotoxicity by UDCA facilitates patient management and may result in better adherence, especially in an out-patient setting.

4. Conclusion

UDCA is a promising therapeutic option for the prevention and treatment of DILI. Further clinical studies are required to validate these results.

Authors' Contributions

All authors have made substantial contributions to: 1) the analysis and interpretation of data; 2) drafting the article or revising it critically for intellectual content; and 3) all authors approved the submitted version to be published.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations Note List

ALT = alanine transaminase

ALP = alkaline phosphatase

AST = Aspartate transaminase

ATD = anti-tuberculosis drug

DILI = drug-induced liver injury

FDA = U.S., Food and Drug Administration

TB = tuberculosis

TID = ter in die (three times a day)

UDCA = ursodeoxycholic acid

ULN = upper limit of normal