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CASE REPORT

Hepatoprotective effects of silymarin in management of liver injury caused by tuberculosis treatment

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Abstract

Tuberculosis (TB) is a chronic infection of global-health concern because of its high incidence, costly medical treatment, drug resistance and risk of co-infections. Anti-TB treatment involves a combination of drugs with high degree of liver toxicity, leading to drug-induced liver injury in 2–28% of patients who receive anti-TB treatment. In this case report, a patient with TB experienced drug-induced liver injury, and the initiation of treatment with silymarin 140 mg three-times daily resulted in a significant hepatoprotective effects as shown by the decreased liver enzyme activity.

This article is part of the *Current clinical use of silymarin in the treatment of toxic liver diseases: a case series* Special Issue: https://www.drugsincontext.com/special_issues/current-clinical-use-of-silymarin-in-the-treatment-of-toxic-liver-diseases-a-case-series

Keywords: case report, deranged liver enzymes, drug-induced liver injury, fatty liver disease, silymarin, tuberculosis treatment.

Citation

Lee YY, Tee V. Hepatoprotective effects of silymarin in management of liver injury caused by tuberculosis treatment. *Drugs Context*. 2023;12:2023-2-11. https://doi.org/10.7573/dic.2023-2-11

Introduction

Tuberculosis (TB) is a chronic infection of global-health concern with a high incidence, costly medical treatment, drug resistance, and risk of co-infections.[1] To effectively treat TB, a combination of bactericidal or bacteriostatic TB drugs, such as ethambutol, isoniazid, rifampicin and pyrazinamide (EHRZ regimen), and streptomycin, is typically required. However, these drugs have high hepatotoxicity[2], with drug-induced liver injury (DILI) being the major anti-TB treatment adverse effect, occurring in 2–28% of patients receiving these medications. Additionally, DILI can lead to non-adherence, treatment failure or drug resistance development.[1,3]

The clinical manifestations of anti-TB DILI vary from asymptomatic mild elevation of liver enzyme activity, for example, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), to acute hepatitis or liver failure, with dominant symptoms appearing as jaundice or hyperbilirubinaemia in acute hepatitis or cholestatic liver disease.[1,4,5] Since DILI generally leads to temporary discontinuation of TB treatment, only after liver function recovery is it possible to restart treatment.[3] Therefore, any intervention accelerating normalization of liver function could be beneficial.[3]

Silymarin is a milk thistle seed extract. Amongst the four flavonolignan isomers that make up silymarin, silybin is the most active and the natural compound most commonly used for the treatment of liver-related diseases globally.[3] Furthermore, silymarin has been found to offer protection against the hepatotoxicity caused by anti-TB drugs.[6] In this case report, a patient with TB experienced DILI, and the potential effectiveness of silymarin (Legalon) in managing liver dysfunction was tested.

Ethics statement

No information is reported that could enable any patient to be identified; therefore, no patient consent to report these cases was required. This manuscript was prepared according to CARE guidelines.

Case report

On 10 April 2017, a 77-year-old male was referred to our department for persistent hyperbilirubinaemia and symptoms, including jaundice, tea-coloured urinary ascites and bilateral leg swelling, approximately 3 months after a few trials of initiation, discontinuation, and switching of anti-TB treatment.

Physical examination 1 week prior (3 April 2017), the patient had undergone oesophago-gastro-duodenoscopy and was diagnosed with antral gastritis.

Concerning recent medical history, the patient had undergone a thorax CT (1 February 2017) showing widespread, scattered cystic bronchiectasis, and fibrosis in both lung fields affecting more the right apicoposterior, the lateral segment of the right middle lobe, and all segments in the right lower lobe, the left upper lobe, left inferior lingual, and the whole left lower lobe. Acalculous cholecystitis, multiple liver cysts, right exophytic simple renal cyst, and lumbar spondylosis were also observed.

Clinical and ultrasound follow-up (17 April 2017) showed a liver homogenously increased in echogenicity and smoothness (liver span measured 14.2 cm) and a well-defined anechoic lesion (1.5×1.3 cm) in segment II in keeping with the liver cyst. Biliary trees were not dilated, the gall bladder was well distended, and there was no calculus or wall thickening. The portal vein was patent and not dilated (7 mm in diameter), the pancreas was normal with no peripancreatic mass or collection, and the spleen was homogeneous with no focal lesions (9.5 cm in length). Moderate ascites in the upper abdomen were observed.

Regarding the anti-TB interventions, TB was initially treated as smear-negative pulmonary TB with an EHRZ regimen (1 January 2017), suspended the following month due to deranged liver enzyme activity. The treatment was then resumed with levofloxacin 500 mg once daily and changed to a regimen with streptomycin, ethambutol and moxifloxacin on 5 March 2017; 2 months later (26 April 2017), streptomycin therapy was disrupted and replaced by Augmentin 1.2 g three-times daily (TDS) a few days after. Within 3 weeks (22 May 2017), the treatment was stopped due to the severity of adverse drug reactions from medications.

At the physician's examination (10 April 2017), hepatomegaly was palpable and jaundice was present. The patient's whole clinical picture suggested that the clinical features were in keeping with fatty liver disease with a simple liver cyst, and biochemical abnormalities were suggestive of DILI due to anti-TB treatment. To manage liver enzyme activity, the patient was prescribed treatment with silymarin 140 mg TDS for 3 months (10 April to 3 July 2017) because no other treatment-suitable options were available, and the patient was not eligible for clinical trials due to his medical conditions.

In routine biochemical and liver function tests (Table 1), altered liver enzyme levels were progressively decreasing, and, at the follow-up visit (17 July 2018), AST and alkaline phosphatase (ALP) levels, in particular, were significantly reduced (Table 1).

The patient's clinical events are summarized in Table 2.

Discussion

The first-line TB standard therapy, recommended by the World Health Organization, consists of using EHRZ regimen.[1]

DILI is the most prevalent and severe complication related to anti-TB treatment, with an incidence ranging from 2% to 28% of treated TB cases.[1,7] The onset of hepatotoxicity can occur within 7–90 days of starting anti-TB treatment.[1] DILI generally cause the temporary interruption of TB treatment due to therapy failure, relapses or drug resistance development.[1,2] If not diagnosed and managed promptly, liver injury can be fatal; thus, it is recommended to monitor liver function regularly in patients receiving anti-TB drugs.[1] Although DILI can resolve spontaneously in most patients, any intervention accelerating the normalization of liver activity may be beneficial.[3]

Over the past two decades, many natural agents, including silymarin and other antioxidants, have been extensively considered.[6] Both preclinical and clinical studies have demonstrated that silymarin, a bioactive extract of milk thistle, has antioxidant and hepatoprotective properties. Legalon is a silymarin formulation with well-characterized pharmacokinetic and pharmacodynamic properties, along with high oral bioavailability.[6]

The effectiveness of silymarin in the prevention and management of DILI from anti-TB treatment has been investigated in several studies, showing a noticeable reduction in the risk of DILI development after 4 weeks of treatment. Additionally, silymarin was found to considerably enhance liver function as evidenced by the reduction of ALT, AST, and alkaline phosphatase (ALP) levels in patients undergoing anti-TB treatment.[6,8] Finally, silymarin, at the recommended dose of up to 420 mg/day, has been shown to be well tolerated, with only minor adverse events documented.[6]

In this case report, DILI occurred within the expected time interval; however, despite changes and disruption

Table 1. Liver function test at baseline and follow-up examinations.

	10/04/2017 – Physician's examination	17/07/2018 – Follow-up
ALT (U/L)	66	71
AST (U/L)	90	51
ALP (U/L)	217	126
TB (μmol/L)	438	154
Alb (g/L)	47	43
Glob (g/L)	30	34

Normal ALT: 7–55 U/L; normal AST: 8–48 U/L; normal ALP: 30–120 U/l; normal TB: 1.7–20.5 μmol/L; normal Alb: 34–54 g/L; normal Glob: 20–35 g/L.
Alb, albumin; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; Glob, globulin; TB, total bilirubin.

Table 2. Relevant data organized as a timeline.

Date	Events
01/01/2017	Initiation of anti-tuberculosis treatment
01/02/2017	Thorax CT: – Widespread, scattered cystic bronchiectasis and fibrosis in both lung fields – Acalculous cholecystitis, multiple liver cysts, right exophytic simple renal cyst and lumbar spondylosis
03/04/2017	Oesophago-gastro-duodenoscopy: – Diagnosis of antral gastritis
10/04/2017	Physician's examination: – The patient was referred with jaundice, tea-coloured urinary ascites and bilateral leg swelling – Hepatomegaly was palpable – Abnormal increased liver enzymatic activity
10/04/2017–03/07/2017	Silymarin 140 mg three-times daily treatment
17/04/2017	Clinical and ultrasound follow-up: – Liver homogenously increased in echogenicity and smoothness with liver cyst
22/05/2017	Disruption of anti-tuberculosis treatment due to the severity of adverse events
17/07/2018	Follow-up examination with significant reduction of liver activity

of the anti-TB regimen, the elevated liver enzyme failed to improve. The turning point was observed upon initiation of silymarin 140 mg TDS, which demonstrated significant hepatoprotective effects on anti-TB DILI, as shown by the decreased serum AST and ALP levels obtained at routine liver function tests and the follow-up visit (Table 1). Additionally, there was a notable reduction in jaundice, a major concern of the patient, along with decrements in terms of bilirubin levels, meaning a significant improvement in cholestasis features. Of note, this reduction in bilirubin levels is in contrast with previous clinical studies, which reported inconsistent effects of silymarin treatment on serum bilirubin levels, with some studies reporting no effects and others reporting increased bilirubin concentrations.[9] In this case report, reduction in serum bilirubin levels following

silymarin treatment may be linked to its anti-inflammatory and antioxidant properties.

These findings support silymarin as a promising supportive intervention aimed at normalizing liver activity during DILI, even when trying to avoid disruption of anti-TB treatment.

The clinical effects of silymarin are likely due to its antioxidant property, acting as a free radical scavenger and affecting the enzyme systems related to the cellular damage.[6] By decreasing oxidative stress and related cytotoxicity, silymarin can protect liver cells that are still intact or not yet irreversibly damaged, making it hepatoprotective. Therefore, to achieve maximum benefit, silymarin treatment should begin as early as possible in patients with DILI, when the regenerative potential of the liver is still high.[6]

Conclusion

DILI associated with anti-TB drugs is a common and severe adverse event. Proper prevention and management of anti-TB DILI is crucial as it affects therapy compliance and effectiveness in patients with TB. This case report highlighted the moderate efficacy and good safety profile of silymarin 140 mg TDS in the management of anti-TB DILI, as it decreased serum AST and ALP levels over treatment without the development of adverse events, along with a notable reduction in jaundice and decrements of bilirubin levels, resulting in general positive effects of silymarin on liver function.

Contributions: All authors contributed equally to the preparation of this manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: The authors declare that they have no conflicts of interest relevant to this manuscript. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2023/04/dic.2023-2-11-COI.pdf

Acknowledgements: Editorial assistance was provided by Francesca Cappellini, PhD, Mattia Zamboni, and Aashni Shah (Polistudium SRL Milan, Italy). This assistance was supported by Viatris Inc.

Funding declaration: Viatris Inc. supported the editorial assistance for this case report.

Article URL: https://www.drugsincontext.com/hepatoprotective-effects-of-silymarin-in-management-of-liver-injury-caused-by-tuberculosis-treatment

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Provenance: Submitted; externally peer reviewed.

Submitted: 20 February 2023; **Accepted:** 13 April 2023; **Published:** 7 June 2023.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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