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Original Article

Correlation of antituberculosis drug-related liver injury and liver function monitoring: A 12-year experience of the Taiwan Drug Relief Foundation

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ABSTRACT

Antituberculosis drug-related liver injury (ATLI) is the most prevalent hepatotoxicity in many countries. Whether monitoring liver tests is beneficial to prevent this potentially grave adverse drug reaction (ADR) is open to debate. The Taiwan Drug Relief Foundation (TDRF) was established by the Taiwan Food and Drug Administration to collect severe cases of ADR and carry out drug injury relief tasks. Our intention was to explore the role of monitoring liver tests in the susceptibility and severity of ATLI from the database of this foundation. All cases of suspected ATLI collected by the TDRF from 1999 to 2012 were reviewed. The basic demographic data, clinical course, and laboratory data of these patients were analyzed. A total of 57 cases with severe ATLI were verified and enrolled into this study. There was a high mortality (71.9%) in this cohort. Twenty-four cases (42.1%) were chronic viral hepatitis B carriers, who had higher baseline serum aminotransferase level than noncarriers. The patients without monitoring liver tests had higher peak serum alanine aminotransferase, bilirubin levels, and mortality (adjusted odds ratio, 8.87; 95% confidence interval = 1.32–59.41; $p = 0.024$) than those with monitoring liver tests. In conclusion, patients with severe ATLI whose records were collected by the TDRF have a high mortality. Patients without follow-up monitoring liver tests had more severe liver injuries and higher mortality than those with monitoring live tests. To alleviate this potentially grave ADR, checking of liver biochemical tests prior to antituberculosis treatment and periodic monitoring of these tests thereafter are highly suggested.

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1. Introduction

Drug-induced liver injury (DILI) is the major cause of acute liver injury in the United States and in many other countries [1,2]. It is also the most common single reason for withdrawing an approved drug in the United States. Many strategies and endeavors have been launched to prevent this inevitable adverse drug reaction (ADR) preclinically and postmarkedly [1]. However, progress in this field seems slow. More efforts should be exerted to mitigate this potentially grave ADR.

Tuberculosis (TB) has recently resurged as a hazardous threat to worldwide public health, which is caused by the growing prevalence of drug-resistant mycobacterium TB strains and the increasing number of acquired immunodeficiency syndrome (AIDS) patients [3]. Regimens containing isoniazid, rifampicin, and pyrazinamide are traditionally used as the first line of therapy for TB. However, hepatotoxicity frequently develops in patients receiving these drugs [4–10]. Antituberculosis drug-related liver injury (ATLI) is the most prevalent DILI in Taiwan and many other countries [4–7]. Chronic hepatitis B infection, which was reported to be a risk factor of ATLI, is also endemic in Taiwan. To prevent this DILI, regular monitoring liver tests was suggested by the Center for Disease Control (CDC), Taiwan, for all TB patients [8]. However, this is only recommended to special high-risk groups, such as patients with chronic viral infection, AIDS, and chronic ethanol consumption, as well as pregnant women in the United States [9]. Whether regular monitoring liver tests is beneficial to prevent ATLI is open to debate.

The Taiwan Drug Relief Foundation (TDRF) has been established by the Taiwan Food and Drug Administration, Department of Health, Taiwan, as a nonprofit organization designated to carry out drug injury relief tasks since 1999 [11]. The premises on which this organization is based are manifold. The core activities of the foundation include issuance of relief payments to the approved claimants, analysis of the causal relationship between injuries and suspected drugs, and research or survey for medication safety-related issues. There have been more than 1,000 applicants for compensation to date. Overall, the top drugs for relief payout in DILI were anti-TB agents [12].

To our knowledge, no study has been conducted to check on the value of monitoring liver tests in identifying grave DILI induced by anti-TB drugs. In addition, most of the previous studies concerning the risk factors of ATLI are retrospective case-control studies or prospective cohort study based on one or a few hospitals or regions [4–10]. The degree of liver injury in these studies ranged from mild to severe. Most of the patients with mild to moderate ATLI may have an "adaptation" to anti-TB agents, which manifests with normalization of liver tests even with continuation of anti-TB treatment [10]. In contrast, the severe form of ATLI may have ominous outcomes despite discontinuing all drugs for TB [4–10]. Therefore, focusing on the severe form of ATLI is a cost benefit in clinical practice and pharmacovigilance. Based on the applicants' database of TDRF, we tried to explore the role of monitoring liver tests in the susceptibility and severity of ATLI.

2. Methods

Those who experienced serious ADR resulting in hospitalization, disability, or death can apply to the TDRF for economic relief. The medical records of all applicants to the TDRF were first scrutinized by two experts, and then reviewed by the board committee sponsored by the Department of Health of Taiwan. All applications with suspected ATLI from 1999 to May 2012 were enrolled into this study.

The inclusion criteria of ATLI were: (1) an increase in serum alanine aminotransferase (ALT) level greater than twice the upper limit of normal value (ULN) during treatment, according to the criteria established by the International Consensus Meeting [13]; (2) a Roussel Uclaf Causality Assessment Method score greater than 5 (when classified as "probable" or "highly probable" drug-induced hepatitis), as derived from the International Consensus Meeting [14].

Patients who had any of the following conditions were excluded from the study: (1) positive serum IgM antibody to hepatitis A virus when ALT or aspartate aminotransferase elevated; (2) other hepatic or systemic diseases that may cause liver dysfunction, such as alcoholic hepatitis, autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, hemochromatosis, stones or tumors of liver and biliary tract, shock, hypoxia, heart failure, and respiratory failure; (3) elevation of serum ALT level less than two times the ULN during anti-TB treatment; (4) insufficient data for assessment.

For evaluating the influence of viral hepatitis infection status to ATLI, hepatitis B and C carriers were enrolled into the analysis. However, the included patients must meet the aforementioned inclusion and exclusion criteria. The definition of hepatitis B and C carriers was positive serum hepatitis B surface antigen or antihepatitis C antibody for more than 6 months.

The latency of a liver injury was regarded as time of drug administration to first abnormal liver tests. To explore the role of monitoring liver tests, patients were divided into two groups. The first group was the monitoring group, which included the patients who had liver biochemical tests at least two times in the first 2 months of anti-TB treatment, or had liver tests at least twice in the 1st month of treatment, if the ATLI occurred in the 1st month. The second group is the nonmonitoring group, which included those without liver biochemical tests after the anti-TB treatment until the occurrence of overt hepatitis. Those patients who had undergone only one-time liver tests after the anti-TB treatment were enrolled into the nonmonitoring group, because one-time liver tests were deemed not sufficient enough, and checking of liver tests in the 2nd, 4th, and 8th weeks after treatment was recommended by the TB guidelines of the Taiwan CDC [8].

This study was approved by the Institutional Review Board of Taipei Veterans General Hospital, and is in accordance with the Helsinki Declaration of 1975.

The Mann–Whitney *U* test and Fisher's exact test were used to compare the variables between groups as appropriate. The multivariate logistic regression test was applied to evaluate the risk factor of mortality (SPSS 19.0 for Windows; SPSS Inc., Chicago, IL, USA). A two-tailed p value below 0.05 was considered statistically significant.