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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.

Table 1 – Clinical characteristics of patients with severe ATLI.

Patient no.	Age/sex	ATT combination	Latency of LFI (wk)	Virus inf./type	Serum examination	LFT before treatment	LFT after treatment	Jaundice
1[a]	71/M	R/I/P/E	2	ND	ND	ND	>5 times	+
2[a]	54/F	R/I/P/E	3.8	+/B	ND	ND	>5 times	+
3[a]	60/M	R/I/P	1.4	+/B	HBsAg(+)	Normal	>5 times	+
4[a]	59/F	R/I/P/E	14.3	+/B	HBsAg(+)	Normal	>5 times	+
5[a]	55/M	R/I/P/E	6	ND	ND	Normal	>5 times	+
6	68/F	R/I/P/E	8	+/C	HBsAg(–) HCV Ab(+)	Normal	>5 times	+
7[a]	41/M	R/I/P/E	12	+/B	HBsAg(+)	ND	>5 times	+
8[a,b]	62/M	R/I/P/E	20	+/B	HBsAg(+)	ND	>5 times	+
9	25/F	R/I/P/E	6	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
10[a]	44/M	R/I/P/E	3	–	HBsAg(–) HCV Ab(–)	Normal	>5 times	+
11[a]	57/M	R/I/P/E	5	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
12[a]	51/F	R/I/P/E	22	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
13	56/M	R/I/P/E	6	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
14[a]	21/M	R/I/P/E	5	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
15	69/F	R/I/P/E	16	–	Anti-HBs Ab(+) Anti-HBc Ab(+)	Normal	>5 times	+
16[a]	82/M	R/I/P/E	3	–	HBsAg(–) Anti-HCV(–)	Normal	>2 times and <3 times	+
17[a,b]	71/M	R/I/P/E	8	+/B	HBeAg(–) Anti-HBe(+)	Normal	>5 times	+
18[a]	63/F	R/I/P/E	6.4	–	HBsAg(–) HBeAg(–) Anti-HCV(–)	Normal	>5 times	+
19[a]	76/M	R/I/P/E	6.1	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
20[a]	75/M	R/I/P/E	3	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
21[b]	55/M	R/I/P/E	13	+/B	HBsAg(+) Anti-HCV(–)	Normal	>5 times	+
22[a,b]	57/M	R/I/P/E	21.3	+/B	HBsAg(+) Anti-HBs(–) Anti-HBC IgM(–)	<2 times normal	>5 times	+
23[a,b]	48/M	R/I/P/E	2	+/B	HBsAg(+) Anti-HCV(–)	Normal	>5 times	+
24[a]	76/M	R/I/P/E	2	+/C	Anti-HCV(+)	>2 times and <3 times	>3 times and <5 times	+
25[a]	54/M	R/I/P/E	5	–	HBsAg(–) HCV Ab(–)	Normal	>5 times	+
26[a]	65/M	R/I/P/E	2	–	HBsAg(–) HCV Ab(–)	Normal	>5 times	+
27[a,b]	52/M	R/I/P/E	8	+/B	HBsAg(+) Anti-HCV(–)	Normal	>5 times	+
28	34/M	R/I/P/E	10	–	HBsAg(–)	<2 times normal	>5 times	+
29[a,b]	51/M	R/I/P/E	10	+/B	HBsAg(+) Anti-HBc(+)	Normal	>5 times	+
30[a]	80/M	R/I/P/E	7	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
31[a]	46/M	R/I/E	4	+/B	HBsAg(+)	Normal	>2 times and <3 times	+
32	72/M	R/I/E	1.2	ND	ND	Normal	>5 times	+
33[a]	68/M	R/I/E	20	+/B	HBsAg(+) HBeAg(–) Anti-HCV(–)	Normal	>5 times	+
34[a,b]	62/M	R/I/P/E	16	+/B	HBsAg(+) HCV-Ab(–)	Normal	>5 times	+

Table 1 – (continued)

Patient no.	Age/sex	ATT combination	Latency of LFI (wk)	Virus inf./type	Serum examination	LFT before treatment	LFT after treatment	Jaundice
35[a]	67/M	R/I/P/E	6	–	HBsAg(–) Anti-HCV(–)	<2 times normal	>5 times	+
36[a,b]	79/M	R/I/P/E	4	+/B	HBsAg(+) HBeAg(–) HCV Ab(–)	<2 times normal	>3 times and <5 times	+
37[a]	53/M	R/I/P/E	0.86	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
38	61/M	R/I/P/E	1.4	–	HBsAg(–) HCV Ab(–)	Normal	>2 times and <3 times	–
39[a,b]	48/M	R/I/P/E	13	+/B	HBsAg(+) Anti-HCV(–)	Normal	>5 times	+
40	49/M	R/I/P/E	25	+/B	HBsAg(+) Anti-HCV(–) HBeAg(–)	Normal	>3 times and <5 times	+
41[a]	59/F	R/I/P/E	15	+/B	HBsAg(+) HBeAg(–) HBeAb(–)	Normal	>5 times	+
42[a,b]	83/M	R/I/P/E	10	+/B	HBsAg(+) HCV-Ab(–)	Normal	>5 times	+
43[a,b]	79/M	R/I/E	5	+/B	HBsAg(+) HCV-Ab(–)	Normal	>5 times	+
44[a]	79/M	R/I/P/E	6	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
45	85/M	R/I/P/E	4	–	HBsAg(–) Anti-HCV(–)	Normal	>3 times and <5 times	–
46[a]	81/M	R/I/E	4	+/B	HBsAg(+) HCV-Ab(–)	<2 times normal	<2 times normal	+
47	4/F	I	12	–	HBsAg(–) HCV Ab(–)	ND	>5 times	+
48	74/M	R/I/P/E	5	–	HBsAg(–) Anti-HCV(–)	<2 times normal	>5 times	+
49[a]	67/M	R/I/P/E	12.4	+/B	HBsAg(+) HBeAg(–)	<2 times normal	>5 times	+
50	79/F	R/I/P	18.4	+/B, C	HBsAg(+) Anti-HCV(+)	ND	>2 times and <3 times	+
51[a]	83/M	R/I/P/E	7.3	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
52[a]	50/M	R/I/P/E	5	–	HBsAg(–)	Normal	>5 times	+
53	42/F	R/I/P/E	5.1	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
54[a]	71/M	R/I/P/E	4	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
55	52/F	R/I/P/E	6.6	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
56[a]	83/M	R/I/P/E	1	–	HBsAg(–) Anti-HCV(–)	Normal	>5 times	+
57	61/M	R/I/P/E	17.6	+/B	HBsAg(+) HBeAg(–)	Normal	>5 times	+

ATLI = antituberculosis drug-related liver injury; ATT = antituberculosis treatment; E = ethambutol; I = isoniazid; LFI = liver function impairment; LFT = liver function test; ND = no available data; P = pyrazinamide; R = rifampicin.

[a] These patients died.

[b] HBV-DBA viral load: ≥100,000 copies/mL.

3. Results

From 1999 to May 2012, there have been 1596 applicants for drug relief in Taiwan. The most frequent ADR was skin disorders, followed by immune system disorders and DILI. Among the 125 cases diagnosed as DILI, the leading culprit drugs were anti-TB agents (57 cases, or 45.6% of all DILI). The clinical characteristics of these 57 patients are shown in Table 1. The male/female ratio of these patients was 3.75 (78.9% vs. 21.1%, Table 2). The patients were relatively old (60.8±16.6 years). Forty-three (75.4%) patients had normal liver biochemical tests prior to the anti-TB treatment. Fifty-two cases (91.2%) had peak serum ALT greater than 5 ULN,

Table 2 – Characteristics of chronic hepatitis B carriers and noncarriers with severe ATLI.

	All patients ($n = 57$)	Hepatitis B carriers ($n = 24$)	Noncarriers ($n = 33$)
Male/Female	45/12	20/4	25/8
Age (y)[a]	60.8 ± 16.6	62.1 ± 12.1	59.1 ± 20.5
Baseline ALT (U/L)[a]	29.4 ± 22.5	35.8 ± 18.0	24.8 ± 24.6[†]
After treatment			
Latency (wk)[a]	8.2 ± 6.2	11.4 ± 6.8	5.8 ± 4.4[†]
Peak serum ALT (U/L)[a]	1304.5 ± 968.3	1458.8 ± 1188.1	1192.3 ± 771.6
Peak serum bilirubin (mg/dL)[a]	22.8 ± 12.4	23.8 ± 11.2	22.0 ± 13.4
Mortality	41 (71.9%)	20 (83.3%)	21 (63.6%)

[†] $p < 0.01$ as compared with hepatitis B carriers.
ALT = alanine aminotransferase; ATLI = antituberculosis drug-related liver injury.
[a] Mean ± standard deviation.

and 41 cases (71.9%) died of hepatic failure. In addition, 24 (42.1%) cases had chronic viral hepatitis B infection and three with chronic hepatitis C infection. In hepatitis B virus (HBV) carriers, 12 patients were positive for HBV DNA when ATLI was diagnosed.

HBV carriers had significantly higher baseline ALT levels and longer latency than the noncarriers ($p < 0.01$, Table 2). However, there was no significant difference in terms of age, sex, peak serum ALT, and bilirubin levels between these two groups. Although HBV carriers had a trend of higher mortality than noncarriers (83.3% vs. 63.6%), the rate did not reach statistical significance.

The comparison between monitoring liver tests group and nonmonitoring group is shown in Table 3. There was no statistical discrepancy in terms of sex, hepatitis virus B infection status, baseline ALT levels, and latency between the two groups. Of note, the nonmonitoring group had higher serum peak ALT and bilirubin levels, and younger age, compared with those in the monitoring group. After adjusting for possible risk factors, nonmonitoring liver test was the only risk factor of mortality in patients with severe ATLI (odds ratio, 8.87; 95% confidence interval, 1.32–59.41; $p = 0.024$; Table 4).

Table 3 – Comparison between monitoring group and nonmonitoring group in patients with severe ATLI.

	Monitoring ($n = 10$)	Nonmonitoring ($n = 47$)	p
Male/female	7/3	38/9	0.445
Age (y)[a]	71.4 ± 11.1	58.6 ± 16.8	0.020
Hepatitis B carrier	6 (60.0%)	18 (38.3%)	0.441
Baseline serum ALT(U/L)[a]	34.3 ± 22.1	28.3 ± 22.8	0.230
After treatment			
Latency (wk)[a]	9.6 ± 7.4	7.9 ± 5.9	0.705
Peak serum ALT (U/L)[a]	702.4 ± 614.9	1432.6 ± 985.8	0.012
Peak serum bilirubin (mg/dL)[a]	15.1 ± 9.4	24.5 ± 12.4	0.019
Mortality	5 (50%)	36 (76.6%)	0.124

ALT = alanine aminotransferase; ATLI = antituberculosis drug-related liver injury.
[a] Mean ± standard deviation.

4. Discussion

ATLI is the most prevalent DILI in many countries [4–10]. It may be serious and may have a fatal outcome. The present national 12 years' cases analysis in Taiwan revealed that severe ATLI had a very high mortality, and patients without monitoring liver tests had more severe liver injuries and poorer outcomes than those with monitoring liver tests.

Prediction or early detection of the high risk patients with ATLI is always a challenging issue to clinicians, pharmacists, and all healthcare providers. One of the approaches used is the application of pharmacogenetics or pharmacogenomics to correlate the genetic polymorphisms of drug-metabolizing enzymes and ATLI [1,7]. Our previous studies have shown that genetic polymorphisms of *N*-acetyltransferase 2, cytochrome P450 2E1, glutathione *S*-transferase M1, and manganese superoxide dismutase (MnSOD, SOD2) may be associated with higher risks of ATLI [15–17]. However, these types of genetic biomarkers warrant further large-scale international studies to validate their real role in the early identification of high-risk groups. Furthermore, these pharmacogenetic assays are still costly and inconvenient for clinical application. We therefore considered that monitoring liver tests may be a simple approach for the early detection and prevention of ATLI.

Regular monitoring liver tests was highly suggested by the Taiwan CDC for all TB patients, which included assaying liver biochemical tests prior to anti-TB treatment and at the 2nd, 4th, and 8th weeks after treatment [8]. Thereafter, the necessity and frequency of monitoring will depend on the status of chronic viral hepatitis infection and clinical condition of the

Table 4 – Multivariate analysis of risk factors for mortality in severe ATLI.

Risk factors	Odds ratio	95% CI	p
Nonmonitoring	8.87	1.32–59.41	0.024
Hepatitis B carrier	4.13	0.89–19.10	0.070
Sex	3.71	0.77–17.84	0.102
Age	1.04	0.99–1.09	0.117

ATLI = antituberculosis drug-related liver injury; CI = confidence interval.

patients. In the United States, monitoring of liver tests is recommended for high-risk groups only, such as patients with chronic viral hepatitis infection, AIDS, and chronic ethanol consumption, and pregnant women [9]. This is attributed to the relatively low incidence of ATLI in the United States, compared with that Taiwan and many other countries. Hepatitis B infection, which is a risk factor for the susceptibility and severity of ATLI in previous reports, is prevalent in Taiwan [4–6]. In the present study, nearly half of the patients were HBV carriers. Thus, the consensus was that patients with chronic viral hepatitis should be followed up with liver tests regularly. However, more than half of our patients were not HBV carriers. Moreover, around 15% patients without hepatitis B or C infection had ATLI in our previous studies [15,16]. Therefore, whether or not the patient is a hepatitis B carrier, the incidence of ATLI is relatively high in Taiwan and many other countries. Because it is difficult to predict who may have grave ATLI, we suggested regular monitoring of liver tests for all patients receiving anti-TB treatment. The present study provides supporting evidence to this recommendation. However, the cost benefit of this approach and the frequency of monitoring liver tests are still debatable. Although further large-scale case-control prospective studies are warranted to elucidate the real role of monitoring, regular assessment of liver tests remains a simple way to ensure the early detection of severe ATLI.

In this study, hepatitis B carriers had higher baseline ALT than noncarriers (35.8 ± 18.0 U/L vs. 24.8 ± 24.6 U/L, $p = 0.001$), which concurs with our expectation. Although hepatitis B carriers had higher mortality (83.3% vs. 63.6%), higher mean peak serum ALT (1,458 U/L vs. 1,192 U/L), and peak serum bilirubin (23.8 mg/dL vs. 22.0 mg/dL) than noncarriers, the rates did not reach statistical significance. The first explanation is that all the patients enrolled in this study had severe DILI, and it may be difficult to further detect the subtle differences of severity between hepatitis B carriers and noncarriers. The second possibility is the limited number of cases included in this study. However, it is not easy and rather time-consuming to collect the verified nationwide severe cases with ATLI in 12 years.

Aged patients have been reported to be more vulnerable to anti-TB drugs [5,8–10,15,16]. The patients in our study were relatively old (60.8 ± 16.6 years), which is consistent with previous reports [5,15,16]. It is noticeable that the patients with monitoring were older than those without monitoring in this study (71.4 vs. 58.6 years, $p = 0.02$). It is probable that healthcare providers may pay more attention to the elderly and evaluating their liver tests more frequently.

Only the severe cases were allowed to apply for drug relief compensation, which explains why this study cohort had a high mortality. The incidence of severe liver injury induced by anti-TB drugs is about 1% in the general population, most of whom may have jaundice [10]. Based on the estimation of Hy's law [18], at least 10% of the severe cases have a dismal outcome or mortality, which is lower than the 72% mortality noted in this study. We believed that many of the severe cases with DILI were not reported to our foundation, and only those involved in very severe or mortality cases may have been motivated to apply for drug relief. Thus, it should be noted that the enrolled patients in this study only represent the most severe of cases, which comprise our target group as part of our efforts to mitigate mortality.

Furthermore, because of the spontaneous nature of these reports, the data from the TDRF in this study cannot be used as an incidence study. Extrapolating the results in this study to the general population is limited and warrants further justification.

In conclusion, patients with severe ATLI by TDRF have a high mortality rate. Patients without monitoring liver tests have more severe liver injuries and higher mortality than those with monitoring liver tests. To mitigate this ominous ADR, checking of liver tests prior to anti-TB treatment, and regular monitoring of liver function thereafter are highly recommended.

Conflicts of interest

The authors have no conflicts of interest relevant to the study and content of this manuscript.

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