J Chin Med Assoc

ORIGINAL ARTICLE

The role of regular liver function monitoring in antituberculosis drug-induced liver injury

Tien-En Chang[a,b], Yi-Shin Huang[a,b,*],Wei-Juin Su[b,c], Chin-Lin Perng[a,b],Yi-Hsiang Huang[a,b], Ming-Chih Hou[a,b]

[a]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC; [c]Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Antituberculosis (TB) drug-induced liver injury (ATLI) is a common adverse effect of anti-TB drugs. Whether regular monitoring of liver function can ameliorate ATLI has been widely debated. The current study aimed to investigate the liver test monitoring status of patients receiving anti-TB treatment in Taiwan, as well as the impact of scheduled liver function monitoring on the risk of ATLI.

Methods: Patients who received anti-TB treatment at our hospital between 2009 and 2017 were enrolled for retrospective analysis.

Results: A total of 1062 patients were included, and of them 469 (44.2%) received regular liver function monitoring (good monitoring group). ATLI was recognized in 100 (9.4%) patients. The good monitoring group detected more ATLI cases early compared with the poor monitoring group (14.7% vs 5.2%, and 21.4 vs 61.6 days, $p < 0.01$), with a lower peak serum alanine aminotransferase (276.1 vs 507.1 IU/L, $p = 0.05$).

Conclusion: In the current study, less than half of all patients who received anti-TB drugs had their liver function monitored regularly. Scheduled monitoring of liver function could facilitate the early identification of more ATLI cases, thus leading to less liver injury. The implementation of periodic liver function monitoring tests in patients receiving anti-TB treatment should be re-emphasized and encouraged.

Keywords: Antituberculosis drug; Drug-induced liver injury; Hepatotoxicity, Tuberculosis

1. INTRODUCTION

Drug-induced liver injury (DILI) is an important adverse effect of antituberculosis (TB) drugs. First-line anti-TB drugs including isoniazid, rifampicin, and pyrazinamide have been shown to have potential hepatotoxicity.[1–4] Anti-TB drug-induced liver injury (ATLI) can range from asymptomatic elevation of aminotransferase to severe hepatotoxicity, or in some cases hepatic failure. Prevention of ATLI is crucial for patient safety and the control of TB. A number of strategies have been proposed to prevent or ameliorate ATLI, including regular monitoring of liver function, the pharmacogenetic approach of detecting high-risk genes for drug metabolizing enzymes, adjustment of anti-TB regimens, and the administration of hepato-protective agents.[1,5–15] Of these suggestions, regular monitoring of liver function seems to be the simplest way of preventing ATLI. However, evidence to support the value of liver function monitoring is sparse, and support for it is based primarily on expert opinion, as opposed to evidence.

*Address correspondence: Dr. Yi-Shin Huang, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: yshuang@vghtpe.gov.tw (Y.-S. Huang).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2019) 82: 535-540.

Received January 29, 2019; accepted March 20, 2019.

doi: 10.1097/JCMA.0000000000000119.

The National Institute for Health and Clinical Excellence (NICE) of the UK, the American Thoracic Society (ATS), and the World Health Organization (WHO) suggest that regular monitoring of liver function is only necessary in patients at high-risk of hepatotoxicity, such as those with baseline liver abnormalities, pre-existing liver disease, chronic alcohol consumption, viral hepatitis, or prior DILI.[6–8] In contrast, the guidelines by the Taiwanese Centers of Disease Control (CDC) recommend checking liver function tests at 2, 4, and 8 weeks after the start of anti-TB treatment in all patients.[5] Regular monitoring of liver function was found to be unnecessary in patients receiving statins, because of their low incidence of hepatotoxicity, even in high-risk patients such as those with viral hepatitis or nonalcoholic fatty liver disease.[16,17] Therefore, whether regular monitoring of liver function in all patients receiving anti-TB treatment is beneficial to prevent ATLI needs to be verified.

The aim of the present study was to investigate the liver test monitoring status of patients receiving anti-TB treatment in Taiwan, and assess the impact of scheduled liver function monitoring on the risk of ATLI.

2. METHODS

2.1. Patients enrolled

All patients who were confirmed of having TB and received treatment at our hospital, a tertiary referral hospital, between 2009 and 2017 were enrolled in the current study.

The inclusion criteria were as follows: (1) patients diagnosed as having an active TB infection, which was verified by a positive acid-fast stain, a nucleic acid amplification test, or

a *Mycobacterium* TB culture; (2) those who received first-line anti-TB therapy; and (3) those completed the whole treatment course at the hospital. The exclusion criteria were as follows: (1) aged <18 years; (2) infected by non-TB mycobacterium or multiple-drug resistance TB; (3) received second-line anti-TB treatment at the beginning; and (4) were lost during follow up.

2.2. Methods

Baseline and follow-up data of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin, creatinine, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV) antibodies, alcohol habits, HIV infection status, concurrent medications, cancer status, and physician adherence to liver function monitoring were analyzed.

The enrolled patients were divided into two groups according to their liver function monitoring status. The good monitoring group included those who received liver function assessment at baseline and the 2, 4, and 8 weeks of treatment, according to the Taiwanese CDC anti-TB guidelines, while patients with incomplete liver function monitoring were assigned to the poor monitoring group.[5]

According to the US Drug-Induced Liver Injury Network (DILIN) criteria, the definition of ATLI was (1) serum ALT or AST greater than five times the upper limit of normal (ULN) among patients with normal baseline liver functions; (2) serum ALT or AST greater than five times the baseline level in patients with abnormal baseline liver functions; (3) serum total bilirubin > 2.5 mg/dL with an elevation of ALT, AST, or ALP and without known hemolysis.[18] A liver abnormality was defined as an increase in serum ALT, AST, ALP, or total bilirubin greater than two times the ULN or baseline.[19]

The severity of ATLI was assessed from grade 1 (mild) to grade 5 (fatal), based on the DILIN index definitions.[18] Active cancer was defined as the existence of vital cancer undergoing any treatment.[20] The ATS risks for ATLI were chronic alcohol consumption, positive HBsAg or anti-HCV, pre-existing liver diseases, current pregnancy, 3 months postpartum, or HIV infection as suggested by the ATS.[1,6]

The present study was approved by the Institutional Review Board of our hospital (approval no. 2017-10-015AC), and was performed in accordance with the Helsinki Declaration of 1975.

2.3. Statistical analysis

Data were expressed as the mean ± SD, except where otherwise stated. Patient parameters between the different groups were examined using a Student's t test or χ^2 test as appropriate. Multivariate logistic regression was used to evaluate the risk of ATLI. All data were analyzed using SPSS 21.0 for windows (SPSS Inc., Chicago, IL, USA). A p value <0.05 was considered to indicate a statistically significant difference.

3. RESULTS

A total of 1062 patients were enrolled in the present study. Their mean age was 67.1 ± 18.8 years, and 748 (70.4%) were male. A total of 106 (10.0%) patients were hepatitis B virus (HBV) carriers and 16 (15.1%) of them received anti-HBV treatment. A total of 43 patients (4%) were hepatitis C carriers and five (11.6%) of them received interferon treatment before their anti-TB treatment. A total of 196 (18.5%) patients had extrapulmonary TB, and the most common type was TB pleurisy (20.4%), followed by lymph node (17.3%) and spine (11.2%) invasion. A total of 105 (9.9%) patients had active cancer, with the most common type being lung cancer (21.9%). The baseline characteristics of all patients are listed in Table 1.

A total of 169 (15.9%) patients had liver abnormalities after their anti-TB treatment, and 100 patients (9.4%) were diagnosed as having ATLI. A total of three patients with liver dysfunction were not considered as ATLI because there were other causes for their elevated liver enzymes, such as autoimmune hepatitis, pancreatic head cancer with obstructive jaundice, and transarterial chemoembolization for hepatocellular carcinoma.

The mean latency of ATLI was 33.8 ± 34.6 days. A total of 21 (21.0%) of the 100 patients with ATLI had severe to fatal DILI. In the study cohort, five patients died from liver injury, 15 patients died from TB, 16 patients died from cancer, and 13 died from other causes. There was no patient who underwent liver transplantation due to ATLI in the study cohort (Table 2).

A total of 469 (44.2%) patients were allocated to the good monitoring group, while 593 (55.8%) patients were allocated to the poor monitoring group. Compared with the poor monitoring group, the good monitoring group had significantly higher baseline serum ALT (p = 0.04) and AST (p < 0.01) levels, and significantly more HBV carriers (12.6% vs 7.9%, p = 0.01) (Table 3). The percentage of patients in the good monitoring group increased significantly year by year (p < 0.01) (Fig. 1). The incidence of both liver abnormalities (23.5% vs 9.9%, p < 0.01) and ATLI (14.7% vs 5.2%, p < 0.01) were significantly higher in the good monitoring group compared with the poor monitoring group. Monitoring status was not associated with ATLI-related mortality (p = 0.11). However, the peak ALT level was lower in the good monitoring group (276.1 ± 346.5 vs 507.1 ± 604.8, p = 0.05) compared with the poor monitoring group. The good monitoring group had a significantly shorter latency time (21.4 ± 25.6 vs 61.6 ± 36.2 days, p < 0.01) compared with the poor monitoring group.

For the management of ATLI, 91 out of 100 patients (91%) had their anti-TB drugs discontinued after ATLI occurred. A total of 80 (80%) of 100 patients were rechallenged using first-line anti-TB drugs after their liver function tests returned to normal or near-normal levels, and 57 (57%) of them were rechallenged successfully. A total of 21 (21%) patients failed to rechallenge the first-line drugs or changed to the second-line regimen upon the ATLI occurred, and only two of them could not endure the second-line therapy (Table 4). There was no significant difference in the management of ATLI between the good monitoring group and the poor monitoring group.

Multivariate logistic regression revealed that positive HBsAg, positive anti-HCV, age > 65 years, disseminated TB, and active cancer were associated with the susceptibility to ATLI (Table 5). Furthermore, positive anti-HCV and age > 65 years were found to increase the risk of severe and fatal ATLI. Active cancer had a trend for increasing the risk of severe and fatal ATLI but its effect was not statistically significant (Table 5).

4. DISCUSSION

ATLI is one of the most common adverse effects of anti-TB treatment. In the present study, it was found that regular liver function monitoring played a crucial role in the detection of ATLI in all patients receiving anti-TB treatment. Furthermore, carriers of HBV, HCV, the elderly, and those with disseminated TB or active cancer were associated with a higher risk of ATLI.

Although it is generally believed that liver function monitoring is important for the prevention and mitigation of ATLI, there was no consensus on how to implement the monitoring strategy. Most guidelines recommend regular monitoring among patients with a higher risk of ATLI. The NICE guidelines suggest monitoring of liver function in patients with coexisting liver disease, abnormal liver functions at baseline, or a history of alcohol misuse or drugs.[7] The WHO recommends monitoring of liver functions in patients with pre-existing liver disease.[8] The ATS

Table 1

Baseline characteristics of the patients receiving antituberculosis treatment

	Total (n = 1062)	ATLI (n = 100)	Non-ATLI (n = 962)	*p*
Age, y	67.1 ± 18.8	70.9 ± 16.5	66.8 ± 19.0	0.02
Male, n (%)	748 (70.4)	67 (67.0)	681 (70.8)	0.43
Normal baseline liver function, n (%)	964 (90.8)	89 (89.0)	875 (91.0)	0.52
Baseline ALT, U/L	22.6 ± 16.0	26.6 ± 19.3	22.1 ± 15.5	0.03
Baseline AST, U/L	25.5 ± 15.7	28.7 ± 19.1	25.2 ± 15.3	0.09
Baseline total bilirubin, mg/dL	0.62 ± 0.41	0.64 ± 0.29	0.62 ± 0.42	0.72
Baseline ALP, U/L	90.4 ± 45.4	95.7 ± 63.9	89.6 ± 42.0	0.36
Baseline creatinine, mg/dL	1.18 ± 1.17	1.33 ± 1.27	1.16 ± 1.16	0.16
Positive HBsAg, n (%)	106 (10.0)	16 (16.0)	90 (9.4)	0.04
Positive Anti-HCV, n (%)	43 (4.0)	9 (9.0)	34 (3.5)	0.01
Habitual alcohol consumption, n (%)	173 (16.3)	18 (18.0)	155 (16.1)	0.63
AIDS, n (%)	15 (1.4)	2 (2.0)	13 (1.4)	0.60
ATS risk,[a] n (%)	352 (33.1)	42 (42.0)	310 (32.2)	0.05
Active cancer, n (%)	105 (9.9)	16 (16.0)	89 (9.3)	0.03
DM, n (%)	226 (21.3)	19 (19.0)	207 (21.5)	0.56
BMI, kg/m^2	21.7 ± 3.7	21.9 ± 3.5	21.6 ± 3.7	0.57
Location of TB				0.09
Pulmonary, n (%)	866 (81.5)	78 (78.0)	788 (81.9)	
Extrapulmonary, n (%)	161 (15.2)	15 (15.0)	146 (15.2)	
Disseminated, n (%)	35 (3.3)	7 (7.0)	28 (2.9)	
Concurrent medications				
Statins, n (%)	63 (5.9)	7 (7.0)	56 (5.8)	0.64
Herbs, n (%)	6 (0.6)	2 (2.0)	4 (0.4)	0.04
NSAIDs, n (%)	46 (4.3)	1 (1.0)	45 (4.7)	0.09
Other potential hepatotoxic drugs, n (%)	10 (1.8)	1 (1.0)	18 (1.9)	0.53

Data were presented as mean ± SD for continuous variables.

Reference value of ALT: 0-40 U/L; AST: 5-45 U/L; ALP: 10-100 U/L; total bilirubin: 0.2-1.6 mg/dL; creatinine: 0.7-1.5 mg/dL.

AIDS = acquired immune deficiency syndrome; ALP = alkaline phosphatase; ALT = alanine transaminase; Anti-HCV = anti-hepatitis C antibody; AST = aspartate transaminase; ATLI = antituberculosis drug-induced liver injury; ATS = American thoracic society; BMI = body mass index; DM = diabetes mellitus; HBsAg = hepatitis B surface antigen; NSAIDs = Nonsteroidal anti-inflammatory drugs; TB = tuberculosis.

[a]ATS risk was defined as patients had either positive HBsAg, anti-HCV, HIV infection, pre-existing liver disease, chronic alcohol consumption, abnormal liver functions at baseline, pregnant, or 3 months postpartum.

Table 2

The liver biochemical data of ATLI in this study

	ATLI (n = 100)
Latency, days	33.8 ± 34.6
Onset	
ALT, U/L	239.8 ± 417.4
AST, U/L	247.5 ± 390.1
ALP, U/L	70.1 ± 118.2
Total bilirubin, mg/dL	2.21 ± 3.21
ALT > 10 × ULN at onset, n (%)	13 (13%)
Time to peak ALT, days	51.3 ± 52.2
Peak	
ALT, U/L	348.5 ± 453.5
AST, U/L	351.7 ± 507.0
ALP, U/L	137.7 ± 194.4
Total bilirubin, mg/dL	5.03 ± 8.86
Peak ALT > 10 × ULN, n (%)	27 (27%)
Severity	
Severe ATLI,[a] n (%)	16 (16%)
Fatal ATLI,[b] n (%)	5 (5%)

Data were presented as mean ± SD for continuous variables.

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; ATLI = antituberculosis drug-induced liver injury.

[a]Severe ATLI: patients with serum total bilirubin ≥ 2.5 mg/dL and have at least one of the following: (1) hepatic failure (INR ≥ 1.5, ascites or encephalopathy); (2) failure of other organs believed to be due to DILI event according to definition of DILIN.

[b]Fatal ATLI: patients died from ATLI or underwent liver transplantation because of ATLI.

recommends regular liver function monitoring in patients with chronic alcohol consumption, viral hepatitis, pre-existing liver diseases, current pregnancy, 3 months postpartum, concurrent use of hepatotoxic agents, or prior DILI or HIV infection.[1,6] On the contrary, the Taiwanese CDC guidelines recommend liver function monitoring in all patients who receive anti-TB treatment, regardless of the patient's baseline liver function or whether they have coexisting liver diseases.[5]

As for the frequency of monitoring, neither NICE nor the WHO mentioned this in their guidelines.[7,8] The ATS suggests checking liver functions at baseline in all patients, and regular monitoring of liver functions every 2 to 4 weeks for the first 2 to 3 months of treatment among high-risk patients.[1] The Taiwanese CDC recommends monitoring of liver functions at baseline and 2, 4, and 8 weeks of treatment.[5] The Taiwanese CDC guidelines were designed to ensure early recognition of ATLI and to prevent grave hepatotoxicity. The present study validated the value of the Taiwanese CDC guidelines, which indicated that regular monitoring of liver functions could detect more ATLI cases earlier with less liver injury.

In the present study, the good monitoring group had a significantly higher rate of baseline liver function abnormality and HBV carriers, which are known to be risk factors for ATLI.[1,21–24] The incidence of disseminated TB was also significantly higher in the good monitoring group. The severity of TB and the existence of risk factors may urge physicians to check liver functions more frequently. However, there were some patients who did not return for liver function tests on time, which may cause

Table 3

Baseline characteristics and ATLI between the good and poor monitoring groups

Characteristics	Good monitoring (n = 469)	Poor monitoring (n = 593)	*p*
Age, y	67.3 ± 18.7	67.0 ± 19.0	0.79
Male, n (%)	311 (66.3)	437 (73.7)	0.01
Normal baseline liver function, n (%)	413 (88.1)	551 (92.9)	0.01
Baseline ALT, U/L	23.7 ± 16.8	21.6 ± 15.3	0.04
Baseline AST, U/L	27.3 ± 16.7	24.2 ± 14.8	<0.01
Baseline total bilirubin, mg/dL	0.64 ± 0.49	0.61 ± 0.34	0.14
Baseline ALP, U/L	93.3 ± 49.5	87.4 ± 40.8	0.19
Baseline creatinine, mg/dL	1.18 ± 1.12	1.18 ± 1.21	0.99
Positive HBsAg, n (%)	59 (12.6)	47 (7.9)	0.01
Positive anti-HCV, n (%)	23 (4.9)	20 (3.4)	0.21
Habitual alcohol consumption, n (%)	78 (16.6)	95 (16.0)	0.75
AIDS, n (%)	8 (1.7)	7 (1.2)	0.47
Active cancer, n (%)	50 (10.7)	55 (9.3)	0.45
DM, n (%)	92 (19.6)	134 (22.6)	0.24
BMI, kg/m^2	21.5 ± 3.7	21.8 ± 3.64	0.32
Location of TB			0.02
Pulmonary, n (%)	386 (82.3)	480 (80.9)	
Extrapulmonary, n (%)	61 (13.0)	100 (16.9)	
Disseminated, n (%)	22 (4.7)	13 (2.2)	
ATLI, n (%)	69 (14.7)	31 (5.2)	<0.01
Onset			
Latency, days	21.4 ± 25.6	61.6 ± 36.2	<0.01
ALT, U/L	188.7 ± 345.1	352.0 ± 533.1	0.13
AST, U/L	215.8 ± 347.7	318.4 ± 470.9	0.24
Total bilirubin, mg/dL	1.89 ± 2.12	2.92 ± 4.82	0.28
Peak			
ALT, U/L	276.1 ± 346.5	507.1 ± 604.8	0.05
AST, U/L	296.1 ± 436.5	475.9 ± 627.9	0.16
Total bilirubin, mg/dL	4.05 ± 4.44	7.20 ± 14.36	0.26
Fatal ATLI, n (%)	4 (0.9%)	1 (0.2%)	0.11

Data were presented as mean ± SD for continuous variables.

AIDS = acquired immune deficiency syndrome; ALP = alkaline phosphatase; ALT = alanine transaminase; Anti-HCV = anti-hepatitis C antibody; AST = aspartate transaminase; ATLI = antituberculosis drug-induced liver injury; ATS = American thoracic society; BMI = body mass index; DM = diabetes mellitus; HBsAg = hepatitis B surface antigen; NSAIDs = Nonsteroidal anti-inflammatory drugs; TB = tuberculosis.

Table 4

Management of liver abnormalities and ATLI in the good monitoring and the poor monitoring groups.

	Good monitoring	Poor monitoring	Total (%)	*p*
Abnormalities of liver tests, n (%)	110 (65.1)	59 (34.9)	169	
Observation, n (%)	20 (18.2)	17 (28.8)	37 (21.9)	0.21
Discontinuation, n (%)	83 (75.5)	37 (62.7)	120 (71.0)	
Adjustment, n (%)	7 (6.4)	5 (8.5)	12(7.1)	
Re-challenge, n (%)	75 (83.3)	35 (83.8)	110 (83.3)	1.00
Re-challenge succeed, n (%)	55 (74.3)	28 (80.0)	83 (76.1)	0.52
Change regimen, n (%)	19 (21.6)	13 (31.0)	32 (24.6)	0.25
Change regimen succeed, n (%)	18 (94.7)	12 (92.3)	30 (93.8)	0.78
ATLI, n (%)	69 (69.0)	31 (31.0)	100	
Observation, n (%)	1 (1.4)	1 (3.2)	2 (2.0)	0.65
Discontinuation, n (%)	64 (92.8)	27 (87.1)	91 (91.0)	
Adjustment, n (%)	4 (5.8)	3 (9.7)	7 (7.0)	
Re-challenge, n (%)	56 (82.4)	24 (82.8)	80 (82.5)	0.96
Re-challenge succeed, n (%)	39 (69.6)	18 (75.0)	57 (71.3)	0.63
Change regimen, n (%)	15 (22.1)	6 (20.0)	21 (21.4)	0.76
Change regimen succeed, n (%)	14 (93.3)	5 (83.3)	19 (90.5)	0.48

Re-challenge: re-challenge the 1st line anti-tuberculosis drugs after liver functions became normal. Change regimen: change to the 2nd line anti-tuberculosis drugs after liver functions became normal or failed to re-challenge the 1st line anti-tuberculosis drugs.

Table 5

Multivariate logistic regression analysis of risk factors for ATLI

	Odds ratios (95% CI)	*p*
Total ATLI		
Positive HBsAg	1.90 (1.05-3.42)	0.03
Positive anti-HCV	2.64 (1.21-5.75)	0.01
Age > 65 y	1.61 (1.03-2.50)	0.04
Disseminated tuberculosis	3.16 (1.31-7.61)	0.01
Active cancer	1.83 (1.01-3.31)	0.05
Severe to fatal ATLI		
Positive HBsAg	1.61 (0.45-5.76)	0.47
Positive anti-HCV	7.59 (2.56-22.52)	<0.01
Age > 65 y	7.36 (1.69-32.15)	<0.01
Disseminated tuberculosis	1.96 (0.23-16.37)	0.54
Active cancer	2.64 (0.91-7.67)	0.07

Anti-HCV = anti-hepatitis C antibody; ATLI = antituberculosis drug-induced liver injury; HBsAg = hepatitis B surface antigen.

underestimation of a physician's adherence. In the present study, it was also noted that the pulmonologist had better adherence to the Taiwanese CDC guidelines, compared with other subspecialists, such as doctors of infectious disease or surgeons (data not shown). There was a significantly shorter latent period in the good monitoring group compared with the poor monitoring group. Also, the percentage of patients in the good monitoring group increased year by year due to improved education and advocacy. The early onset of liver dysfunction often leads to a close follow-up and may prevent progression to ATLI. Asymptomatic ATLI may be missed in the poor monitoring group, which can cause underestimation of the incidence of ATLI. Regular monitoring of liver function seems to increase the detection rate of ATLI.

Chih et al[14] analyzed severe ATLI patients who reported to the Taiwan Drug Relief Foundation and found that the nonmonitoring group had more severe hepatotoxicity and a higher mortality rate compared with the monitoring group. Another retrospective cohort studied by Wu et al[15] revealed that scheduled monitoring could reduce hospitalization rates and was thought to lessen hepatotoxicity and reduce mortality. However, the current study could not verify the association between monitoring status and ATLI-related mortality. The possible reasons for this discrepancy were as follows: (1) Chih's study included patients who reported voluntarily, while Wu's study only enrolled patients with ATLI. Neither of these previous studies included consecutive patients as in the present study; (2) Chih's study included cases with more severe liver injuries than those included in the present study; (3) The patients in the current study were older than those in the other studies, which may have influenced the results; and (4) The mortality rate in the current study was too low to be statistically significant.

Chih et al[14] revealed a mean latency of 8.2 weeks in all ATLI patients. A recent study by Abbara et al[25] in the UK found that the median latency for ATLI was 12.5 days, and 87.6% occurred within 8 weeks. In the REMoxTB study in the UK, ATLI was recognized in 58 of the 1928 (3.0%) included patients at a median time of 28 days.[26] In a retrospective study in Korea, 67.6% patients developed ATLI within 30 days.[27] The mean latency of 33.8 ± 34.6 days observed in the present study was in agreement with these previous findings, and supports the

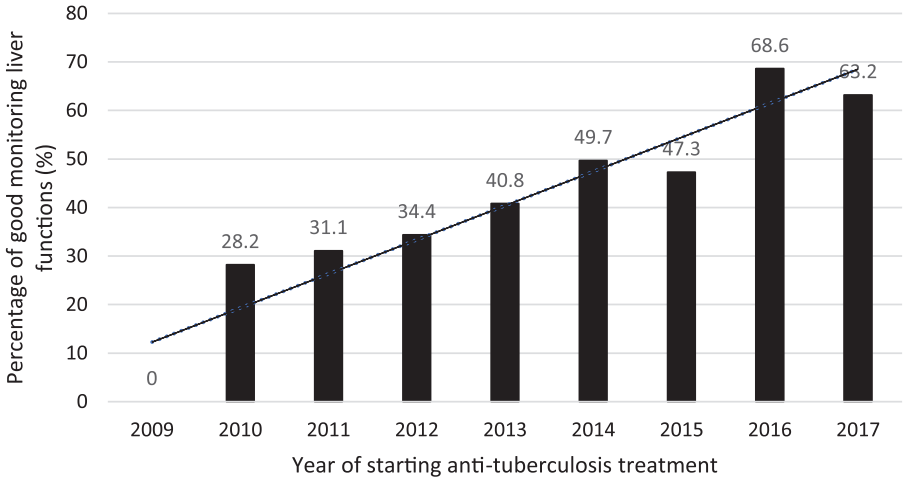

Fig. 1 The increasing trend of percentage of patients with good monitoring to liver function from 2009 to 2017; *$p < 0.01$ by χ^2 test for trend.

current guidelines from the ATS and the Taiwanese CDC that scheduled liver function monitoring should be implemented in the first 2 months of treatment.[5,6]

The present study found that patients aged >65 years ($p < 0.01$) and with positive anti-HCV ($p < 0.01$) had a significantly higher risk of severe and fatal ATLI, which was comparable with previous studies.[1,21–24,28] Therefore, regular surveillance of liver functions is highly recommended in these high-risk patients.

Patients with coexisting active cancer were also found to have a higher risk of ATLI in the current study; however, the reason why these patients were vulnerable to ATLI is unknown. Abnormality of the immune system, poor nutrition status, and coadministration of chemotherapeutic agents in these patients may augment liver injury.[1]

Good monitoring can increase the detection of ATLI among all patients, which supports the policy suggested by the Taiwanese CDC. Although the mortality rates in the good monitoring and poor monitoring groups were similar, this was probably due to early discontinuation of anti-TB drugs in patients with ATLI and the limited number of expired cases.

There were some limitations to the present study. First, the amount of alcohol consumption and comorbidities may not have been accurately recorded, which could interfere with the designation of the patient's susceptibility to hepatotoxicity. Second, the incidence of ATLI in the poor monitoring group may have been underestimated since asymptomatic ATLI could be missed without regular surveillance. Third, the study was a retrospective study, not a prospective one. As the study aimed to assess the adherence of physician's to Taiwanese CDC guidelines, the prospective study did not meet the aimed requirements and was not ethical.

In conclusion, in the current study less than half of the patients who received anti-TB drugs received regular monitoring of their liver function. Scheduled liver function monitoring could enable the early identification of more ATLI cases, and therefore results in less liver injury. The implementation of periodic liver function monitoring tests in patients receiving anti-TB treatment should be re-emphasized and encouraged.

ACKNOWLEDGMENTS

This study was supported by the grand from Taipei Veterans General Hospital (V108C-007, V108A-008).

We thank tuberculosis case manager, Chiao-Ping Li and study nurse, Dai-Ling Lin.

REFERENCES

1. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al.; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;**174**:935–52.
2. Huang YS, Chern HD, Su WJ, Wu JC, Lai SL, Yang SY, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. *Hepatology* 2002;**35**:883–9.
3. Huang YS. Recent progress in genetic variation and risk of antituberculosis drug-induced liver injury. *J Chin Med Assoc* 2014;**77**:169–73.
4. Chitturi S, Farrell G. Drug-induced liver disease. In: Schiff ER, Maddrey WC, Sorrell MF, editors. *Schiff's diseases of the liver.* 11th ed. New Jersey: Wiley-Blackwell; 2011, p. 703–83.
5. Centers for Disease Control, Ministry of Health and Welfare, R.O.C. (Taiwan). Taiwan guidelines for TB diagnosis and treatment, 6th edition. Available at https://www.cdc.gov.tw/english/infectionreportinfo.aspx?treeid=3847719104be0678&nowtreeid=3112320c3b647165&tid=2346C8B39500C908
6. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official american thoracic society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis* 2016;**63**:e147–95.
7. National Collaborating Centre for Chronic Conditions; Centre for Clinical Practice at NICE. *National Institute for Health and Clinical Excellence: guidance. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control*. London: National Institute for Health and Clinical Excellence; 2011.
8. World Health Organization, and Stop TB Initiative (World Health Organization). *Treatment of tuberculosis: guidelines*. 4th ed. Geneva: World Health Organization; 2010.
9. Aithal GP. Pharmacogenetic testing in idiosyncratic drug-induced liver injury: current role in clinical practice. *Liver Int* 2015;**35**:1801–8.
10. Jung JA, Kim TE, Lee H, Jeong BH, Park HY, Jeon K, et al. A proposal for an individualized pharmacogenetic-guided isoniazid dosage regimen for patients with tuberculosis. *Drug Des Devel Ther* 2015;**9**:5433–8.
11. Mushiroda T, Yanai H, Yoshiyama T, Sasaki Y, Okumura M, Ogata H, et al. Development of a prediction system for anti-tuberculosis drug-induced liver injury in Japanese patients. *Hum Genome Var* 2016;**3**:16014.
12. Saito Z, Kaneko Y, Kinoshita A, Kurita Y, Odashima K, Horikiri T, et al. Effectiveness of hepatoprotective drugs for anti-tuberculosis drug-induced hepatotoxicity: a retrospective analysis. *BMC Infect Dis* 2016;**16**:668.
13. Singanayagam A, Sridhar S, Dhariwal J, Abdel-Aziz D, Munro K, Connell DW, et al. A comparison between two strategies for monitoring hepatic function during antituberculous therapy. *Am J Respir Crit Care Med* 2012;**185**:653–9.

14. Chih LH, On AWF, Huang YS. Correlation of antituberculosis drug-related liver injury and liver function monitoring: a 12-year experience of the Taiwan drug relief foundation. *J Food Drug Anal* 2014;**22**:356–62.
15. Wu S, Xia Y, Lv X, Zhang Y, Tang S, Yang Z, et al. Effect of scheduled monitoring of liver function during anti-tuberculosis treatment in a retrospective cohort in china. *BMC Public Health* 2012;**12**:454.
16. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology* 2004;**126**:1287–92.
17. Khorashadi S, Hasson NK, Cheung RC. Incidence of statin hepatotoxicity in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2006;**4**:902–7; quiz 806.
18. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al.; DILIN Study Group. Drug-induced liver injury network (DILIN) prospective study: rationale, design and conduct. *Drug Saf* 2009;**32**:55–68.
19. Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol* 1990;**11**:272–6.
20. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al.; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;**349**:146–53.
21. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. *Respirology* 2006;**11**:699–707.
22. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008;**23**:192–202.
23. Hosford JD, von Fricken ME, Lauzardo M, Chang M, Dai Y, Lyon JA, et al. Hepatotoxicity from antituberculous therapy in the elderly: a systematic review. *Tuberculosis (Edinb)* 2015;**95**:112–22.
24. Wang NT, Huang YS, Lin MH, Huang B, Perng CL, Lin HC. Chronic hepatitis B infection and risk of antituberculosis drug-induced liver injury: systematic review and meta-analysis. *J Chin Med Assoc* 2016;**79**:368–74.
25. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infect Dis* 2017;**17**:231.
26. Tweed CD, Wills GH, Crook AM, Dawson R, Diacon AH, Louw CE, et al. Liver toxicity associated with tuberculosis chemotherapy in the remoxtb study. *BMC Med* 2018;**16**:46.
27. Lee CM, Lee SS, Lee JM, Cho HC, Kim WS, Kim HJ, et al. Early monitoring for detection of antituberculous drug-induced hepatotoxicity. *Korean J Intern Med* 2016;**31**:65–72.
28. Chang TE, Huang YS, Chang CH, Perng CL, Huang YH, Hou MC. The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: a systematic review and meta-analysis. *J Chin Med Assoc* 2018;**81**:111–8.