Antituberculosis Drug-induced Liver Injury in Children

Incidence and Risk Factors During the Two-month Intensive Phase of Therapy

Fajri Gafar, MPharm,† Helmi Arifin, PhD,† Yusri D. Jurnalis, MD, PhD,‡ Finny F. Yani, MD, PhD,‡ Najmiatul Fitria, MPharm,*† Jan-Willem C. Alffenaar, PharmD, PhD,§ and Bob Wilffert, PhD*§*

Background: As one of the most frequent and serious adverse reactions during tuberculosis (TB) treatment, antituberculosis drug-induced liver injury (ATLI) in children has been studied insufficiently compared with adults. We aimed to determine the incidence and risk factors of ATLI in children during the first 2 months of TB therapy.
Methods: A total of 41 children with TB and treated with first-line anti-TB drugs were prospectively followed-up for the development of ATLI. Liver function tests were performed at baseline and after 2 weeks of therapy. Subsequent tests were conducted at 4, 6 and 8 weeks if the initial 2-week measurement was abnormal or if symptoms of hepatotoxicity were reported.
Results: ATLI was detected in 11 (27%) patients within 14 to 42 days from the start of therapy, with most of them (54%) occurred after 2 weeks. TB treatment was stopped immediately in 6 of 11 patients who developed ATLI, and no recurrent hepatotoxicity after drug reintroductions in these patients. Univariate analysis showed that ATLI was significantly associated with TB meningitis ($P < 0.01$), hypoalbuminemia ($P < 0.05$) and hepatotoxic comedications ($P < 0.01$). Age, sex, nutritional status, HIV status and baseline liver function abnormalities were not associated with ATLI. Multivariate analysis identified hypoalbuminemia and hepatotoxic comedications (both $P < 0.1$) tend to be independently associated with ATLI.
Conclusions: Children with hypoalbuminemia and use of hepatotoxic comedications are suggested to be monitored closely for the development of ATLI.

Key Words: tuberculosis, antituberculosis drugs, drug-induced liver injury, children, risk factors

(*Pediatr Infect Dis J* 2019;38:50–53)

Approximately 10.4 million people developed tuberculosis (TB) worldwide in 2016, of which 1 million (10%) are children. Furthermore, there are 1.3 million cases of TB deaths, with 82% of them occurring in low- and middle-income countries mostly in Africa and South-East Asia.[1] Antituberculosis drug-induced liver injury (ATLI) is one of the most frequent and serious adverse reactions during TB treatment.[2] Isoniazid, rifampicin and pyrazinamide are the most potentially hepatotoxic first-line anti-TB drugs, whereas ethambutol and streptomycin have no known hepatotoxicity reactions.[3]

ATLI has a significant role in diminishing treatment effectiveness by increasing patient morbidity and mortality and disrupting therapy adherence.[4,5] As an independent predictor of prolonged TB treatment,[6] the high occurrence of ATLI results in discontinuation of therapy and potentially treatment failure. In adults, various factors, such as advanced age, female sex, malnutrition, HIV/AIDS, preexistent liver disease (eg, hepatitis B/C infections), alcohol intoxication, hepatotoxic comedications and genetics, are reported to be associated with higher risk to develop ATLI.[3]

The incidence and factors associated with ATLI in children have been studied insufficiently compared with adults. Even though the incidence of ATLI is lower than in adults, ATLI can develop in children at any age or any dosage of anti-TB drugs, with signs and symptoms are frequently ignored in many cases.[7] Similarly, data about ATLI in the Indonesian pediatric population are limited. An earlier study in Indonesia reported that the rate of ATLI in children was about 7.4%.[8] In the study, liver function tests (LFTs) were only performed in the first 2 weeks of therapy so that the actual incidence of ATLI was underestimated. Based on the 2014 World Health Organization guideline on the management of TB in children, routine monitoring of liver functions is not mandatory during TB treatment. It is only recommended if liver tenderness, hepatomegaly or jaundice occur during therapy.[9] In addition, according to the national guidelines for childhood TB by the Indonesian Pediatric Society (IDAI), LFTs are only performed if hepatic dysfunction is suspected before the treatment, or symptoms of hepatotoxicity (eg, jaundice) appear during therapy.[10] In this context, this study aims to determine the incidence and risk factors associated with ATLI in Indonesian pediatric patients during the first 2 months (ie, the intensive phase) of TB treatment.

PATIENTS AND METHODS

We conducted a prospective observational study at the Department of Child Health of the M Djamil Hospital in Padang, Indonesia, from September 2015 to April 2016. All consecutive inpatients or outpatients from 1 to 15 years of age, diagnosed with active pulmonary TB or extra-pulmonary TB and treated with isoniazid, rifampicin and pyrazinamide with/without ethambutol were eligible for inclusion in this study. TB was clinically diagnosed using the pediatric TB scoring system developed by the IDAI (Table, Supplemental Digital Content 1A, http://links.lww.com/INF/D280).[10] Other procedures such as cerebrospinal fluid analysis and head computed tomographic scan to confirm TB meningitis (TBM) were performed if applicable.

Patients were treated by pediatricians of the M Djamil Hospital and were excluded if they had suspected multidrug resistance TB or low adherence and failure to complete the treatment. Patients with suspected pre-existing liver diseases before starting

Accepted for publication August 16, 2018.
From the *Unit of PharmacoTherapy, Epidemiology and Economics, Groningen Research Institute of Pharmacy and §Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; and †Faculty of Pharmacy, Unit of Pharmacology and Clinical Pharmacy and ‡Faculty of Medicines, Department of Child Health, M. Djamil Hospital, Andalas University, Padang, Indonesia.
This research was supported by the Indonesia Endowment Fund for Education (LPDP) from the Ministry of Finance, Republic of Indonesia. LPDP was in no way involved in study design, writing or reviewing of the manuscript.
The authors have no conflicts of interest to disclose.
Address for correspondence: Fajri Gafar, MPharm, Unit of PharmacoTherapy, Epidemiology and Economics, Groningen Research Institute of Pharmacy, University of Groningen, Antonius Deusinglaan 1, Building 3214, Room 0450, 9713 AV Groningen, The Netherlands. E-mail: f.gafar@rug.nl.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/19/3801-0050
DOI: 10.1097/INF.0000000000002192

medication such as baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) more than 3× the upper limit of normal (ULN), viral hepatitis B/C or clinical symptoms like hepatomegaly and jaundice were also excluded.[3] Suspected viral hepatitis B and/or C infections were defined by anamnesis of the clinical history, including perinatal transmission, blood transfusion history, sexual contact, infected household contact and direct percutaneous exposure to blood. All TB patients were screened and tested for HIV, and all HIV coinfected patients were initially treated with anti-TB drugs only and had not started antiretroviral therapy until the completion of the intensive phase of therapy. Other comedications concomitantly used with anti-TB drugs were evaluated with the LiverTox Database for detailed information on drugs potentially causing drug-induced liver injury.[11]

Treatment Protocol

During the first 2 months of therapy, patients received a drug combination regimen based on the 2013 IDAI guideline in accordance with the 2014 World Health Organization guidance for the national TB programs on the management of TB, consisting of isoniazid, rifampicin and pyrazinamide for pulmonary TB and lymphadenitis TB; or isoniazid, rifampicin, pyrazinamide and ethambutol for extensive pulmonary TB, TB meningitis and osteoarticular TB.[9,10] The drug doses are described in the Table, Supplemental Digital Content 1B, http://links.lww.com/INF/D280.

Data Collection

Demographic data and clinical history were collected at pretreatment for each patient. Nutritional status was assessed by measuring length/stature-for-age and weight-for-age percentiles based on the 2000 Centers for Disease Control and Prevention Growth Charts.[12] LFTs, including ALT, AST and total bilirubin, were performed at baseline and 2 weeks after initiation of therapy. Subsequent ALT, AST and total bilirubin were taken at 4, 6 and 8 weeks if the initial 2-week measurement was abnormal or if symptoms of hepatotoxicity such as anorexia, nausea, vomiting, abdominal pain or jaundice were reported.[13] The reference normal values in our laboratory are ALT, <41 IU/L (male) and <31 IU/L (female); AST: <38 IU/L (male) and <32 IU/L (female); total bilirubin <1 mg/dL; serum albumin >3.7 g/dL.

Diagnosis and Management of ATLI

ATLI was defined as elevation of ALT/AST to more than 3× the ULN. To stop TB treatment caused by ATLI, at least one of the following criteria must be fulfilled: (1) elevation of transaminase levels >3× the ULN with clinical symptoms of hepatotoxicity (nausea, vomiting, abdominal pain and jaundice) or >5× the ULN without the presence of symptoms; and (2) a rise in total bilirubin to more than 2 mg/dL in the presence of jaundice, both with normalization of liver enzymes and resolving of symptoms of hepatotoxicity after withdrawal of all anti-TB drugs.[3,14,15] For those who stopped TB treatment, liver functions were measured weekly until the symptoms resolved, and transaminase levels declined to less than 2× the ULN. As suggested by the IDAI guideline, the original regimen was restarted simultaneously when the symptoms and liver enzymes normalized. Patients who have increased transaminases >3× the ULN without the presence of symptoms of hepatotoxicity still continued the treatment with closely followed-up.[10]

Statistical Analysis

Demographics and clinical factors considered for the study were age, sex, nutritional status, type of TB, albumin status, HIV status, concomitant hepatotoxic drugs and baseline LFTs, including ALT, AST and total bilirubin. These variables were analyzed univariately using χ^2/Fisher exact test to identify risk factors for ATLI. Multivariate binary logistic regression analysis was then used to identify independent risk factors for the development of ATLI. All variables with P value <0.2 in the univariate analysis with numbers in both exposed and nonexposed groups >25% were included in multivariate analysis. Statistical significance was accepted at $P < 0.05$. All data were analyzed with IBM SPSS Statistics version 23.0.

Ethical Consideration

Ethical clearance was granted by the Research Ethics Committee, Faculty of Medicines, Andalas University (No: 076/KEP/FK/2015). Written informed consent was obtained from parents/guardians before the commencement of the study.

RESULTS

Forty-nine patients were screened and included in the study. Eight of these were excluded from analysis; 3 patients had withdrawn from the study and 5 patients had incomplete clinical data due to technical problems during laboratory measurements (n = 2), and 3 patients diagnosed with TBM died within the first 2 weeks of treatment due to severity of the disease before the LFTs could be measured. Of the 41 patients available for analysis, there were 11 and 14 patients with abnormal ALT and AST, respectively. Among them, there were 2 patients with baseline ALT >2× the ULN and 3 patients with AST >2× the ULN. None of those who have baseline transaminases above 2× the ULN then developed into ATLI. Patient characteristics of the study population are presented in Table, Supplemental Digital Content 2, http://links.lww.com/INF/D281.

During the first 2 months of therapy, ATLI was detected in 11 (26.8%) patients within 14 to 42 days from the start of treatment. Six patients developed ATLI after 2 weeks of treatment, 3 patients developed ATLI after 4 weeks and 2 patients after 6 weeks. Of the 11 patients who developed ATLI, 5 increased in both ALT and AST, 3 increased in AST, 2 increased in ALT and 1 rose in bilirubin. All of the patients who developed ATLI were considered to have a stable condition including 9 inpatients with TBM and 2 outpatients with pulmonary TB.

There were 6 of 11 patients (5 with TBM and 1 with pulmonary TB) in which all anti-TB drugs were stopped immediately. Among them, 3 patients with both ALT and AST >3× the ULN showed the symptoms of fever and nausea (2 patients); and nausea, vomiting as well as abdominal pain (1 patient). Two patients both experienced fever with ALT/AST >5× the ULN developed ATLI without other specific symptoms of hepatotoxicity. The remaining 1 patient who rose in bilirubin >2 mg/dL experienced jaundice and anorexia. Both clinical symptoms and liver function profiles resolved within 1 week in 5 patients and within 2 weeks in the other one. After reintroducing anti-TB drugs, we performed LFTs fortnightly for all those 6 patients, and no ATLI recurrence was observed until the completion of the study.

The univariate analysis, shown in Table 1, demonstrated that TBM [$P = 0.003$; odds ratio (OR): 12.37; 95% confidence interval (CI): 2.18–69.99], hypoalbuminemia ($P = 0.029$; OR: 6.22; 95% CI: 1.33–29.01) and hepatotoxic comedications ($P = 0.001$; OR: 20.00; 95% CI: 2.24–178.94) were significantly associated with ATLI. Sex, age, nutritional status, HIV status and abnormality of baseline LFTs (ALT, AST and total bilirubin) had no significant association with ATLI. Multivariate logistic regression analysis identified hypoalbuminemia ($P = 0.083$; OR: 5.31; 95% CI: 0.80–35.21) and concomitant hepatotoxic drugs ($P = 0.078$; OR: 12.74; 95% CI: 0.75–216.12) tend to be independently associated with ATLI but not found statistically significant (Table 2). Potential hepatotoxic comedications used by patients who developed ATLI

TABLE 1. Risk Factors Associated With ATLI Using Univariate Analysis

	ATLI Patients (n = 11)	Non-ATLI Patients (n = 30)	OR (95% CI)	*P* Value
Female	5 (45.5)	10 (33.3)	1.67 (0.41–6.82)	0.491
Age 1–5 years	6 (54.5)	12 (40.0)	1.80 (0.45–7.25)	0.489
Underweight	9 (81.8)	16 (53.3)	3.94 (0.73–21.38)	0.152
TB meningitis	9 (81.8)	8 (26.7)	12.37 (2.18–69.99)	0.003*
Hypoalbuminemia	8 (72.7)	9 (30.0)	6.22 (1.33–29.01)	0.029*
Hepatotoxic comedications	10 (90.9)	10 (33.3)	20.0 (2.24–178.94)	0.001*
Abnormal baseline ALT	4 (36.4)	7 (23.3)	1.88 (0.42–8.34)	0.445
Abnormal baseline AST	5 (45.5)	9 (30.0)	1.94 (0.47–8.05)	0.463
Abnormal baseline total bilirubin	3 (27.3)	1 (3.3)	10.88 (0.99–119.24)	0.052
HIV positive	1 (9.1)	3 (10.0)	0.90 (0.08–9.69)	1.000

Data are presented as number (percentages).

TABLE 2. Independent Risk Factors Associated With ATLI Using Multivariate Analysis

	B	Adjusted OR (95% CI)	*P* Value
Underweight	0.99	2.70 (0.34–21.69)	0.350
TB meningitis	0.74	2.09 (0.19–22.63)	0.554
Hypoalbuminemia	1.67	5.31 (0.80–35.21)	0.083
Hepatotoxic comedications	2.54	12.74 (0.75-216.12)	0.078

B indicates logistic regression coefficients.

were phenobarbital in 7 (63.6%), paracetamol in 5 (45.4%), omeprazole in 2 (18.2%), ranitidine in 2 (18.2%), phenytoin in 1 (9.1%) and captopril in 1 (9.1%) patients.

DISCUSSION

In our study, 27% of the patients were categorized as having ATLI and 15% stopped TB treatment caused by ATLI. This result was higher than reported in recent similar studies of children, such as in Indonesia (7.4%),[8] in Japan (8.1%)[16] and in India (15.2%).[17] This higher incidence could be related to transient and asymptomatic elevations of transaminases, most of which represents hepatic adaptation with spontaneous resolution.[14] As drug reintroduction regimens were well-tolerated in those who developed ATLI, it was likely that the initial hepatotoxic event could have been the result of hepatic adaptation. Because there is no golden standard to distinguish between true ATLI and hepatic adaptation, patients who had treatment interrupted in our study were more likely of concern for evolving ATLI rather than because of established hepatotoxicity. However, treatment discontinuation based on biochemical thresholds and symptoms monitoring as suggested by standard guidelines would benefit to prevent severe progression of hepatic failure at an earlier stage.[18]

More patients in our study developed the clinical manifestation of nausea, and only few patients had jaundice, vomiting, anorexia and abdominal pain, which were the most frequent symptoms occurring in other studies.[19,20] Notably, 7 patients who developed ATLI in our study (including 2 patients who stopped TB treatment) were asymptomatic or had prodromal symptoms (eg, fever). Shang et al[20] showed that a third of their patients who developed ATLI were asymptomatic, including patients with severe hepatotoxicity. In some cases, severe hepatotoxicity may have progressed into liver failure requiring liver transplantation.[21,22] As severe hepatotoxicity can occur without clinical symptoms, routine monitoring has proven to be effective in identifying asymptomatic liver damage reducing the need for hospitalization.[23]

The higher incidence of ATLI in children with TBM was supported by Donald[7] who showed that abnormal LFTs and jaundice were recorded, respectively, in 53% and in 10% of children during TB therapy. The reason why patients with TBM are more likely to have ATLI compared with other types of TB is still unclear but could be related to severity of the underlying disease.[24] In addition, all patients with TBM in our study had used potentially hepatotoxic comedications, such as paracetamol and phenobarbital. Other studies also showed an association between hepatotoxic comedications with ATLI.[25,26]

The higher risk of hepatotoxicity in patients with hypoalbuminemia may be related to depletion of glutathione stores, making patients more vulnerable to oxidative injuries and disrupting hepatic drug metabolism.[19] It seems that malnutrition as identified by hypoalbuminemia itself might be the sign of hepatic dysfunction, and the possibility that it was partly caused by liver damage cannot be ruled out. However, it is unlikely that this short term of hepatotoxicity would have resulted in hypoalbuminemia as both clinical symptoms and liver function profiles resolved in all patients after stopping TB treatment, and no recurrent hepatotoxicity after drug reintroductions. Several previous studies also reported malnutrition including hypoalbuminemia and low Body Mass Index (BMI) to be associated with increased ATLI.[19,25,27,28]

Many studies reported that patients who are at higher risk of developing ATLI are associated with female sex, younger age (<5 years), abnormal baseline LFTs and HIV positive.[3,14] Nevertheless, we did not find similar results. Several possible mechanisms could be responsible for these differences, such as sample size, variations of pharmacokinetics and genetics.

Our study has several limitations that should be considered. Because all of the patients were diagnosed clinically instead of bacteriologically confirmed with TB, there was still a possibility of diagnosis interchange between latent TB infection and TB disease. This aspect could limit reproducibility and extrapolation of the results. Our diagnostic tool (IDAI TB scoring system) also needs to be confirmed in studies with diverse population before it can be generalized. We acknowledge that baseline elevation of transaminases above the ULN but below the exclusion threshold of 3× the ULN could be the sign of pre-existing hepatic dysfunctions. However, there was no firm diagnosis that could explain these abnormalities in our study as we only excluded the possibility of viral hepatitis B or C coinfections by clinical anamnesis and were not able to test for viral hepatitis biomarkers. Because Indonesia is reported to have a moderate to high incidence of hepatitis B, and governmental pediatric vaccination against hepatitis B virus was only started since 1997, mothers of the included children were probably not immunized against it.[29] If the mother was infected and transmitted the virus before the child got vaccinated, and no hepatitis B immunoglobulin was simultaneously administered within 24 hours of birth, the child would not be protected by vaccination. This possibly resulted in misclassification of viral hepatitis to ATLI in some patients.

Apart from the relatively small sample size of patients which limits the power of the study, we monitored the liver functions only for the first 2 months of TB treatment. Although hepatotoxicity most often occurs in the first 2 months, the actual eventual hepatotoxicity rate by the end of therapy could be higher. Our method was also unable to clearly clarify asymptomatic hepatotoxicity after 2 weeks as LFTs at 4, 6 and 8 weeks were only performed for patients with symptomatic disease. Then, we acknowledge that AST is not as specific as ALT to determine hepatotoxicity related to anti-TB drugs although both ALT and AST have been used as biomarkers of ATLI in various studies.[3] The increase of AST alone cannot clearly define hepatocellular injury and may lead to the inclusion of patients without ATLI. Therefore, our exclusion criteria, specific monitoring of LFTs and a low threshold for defining hepatotoxicity potentially resulted in an underestimation of ATLI. Further studies with larger sample sizes over a longer time frame would provide a clearer picture of ATLI in children.

In conclusion, the incidence rate of ATLI in children treated with anti-TB drugs is quite high. Patients with hypoalbuminemia and those who use concomitant hepatotoxic drugs are suggested to be monitored closely for the development of ATLI. These findings can aid clinicians to be aware of the problem particularly in patients with hypoalbuminemia and benefit for patients who could avoid hepatotoxic comedications during TB therapy.

ACKNOWLEDGMENTS

The authors thank all the patients for their participation in the study and the pediatricians, pediatric residents as well as nursing staff at the Department of Child Health of the M. Djamil Hospital for their assistance during the follow-up of these patients. We also thank the Indonesia Endowment Fund for Education (LPDP) for their purely financial support.

REFERENCES

1. World Health Organization (WHO). *Global Tuberculosis Report 2017*; 2017.
2. Yee D, Valiquette C, Pelletier M, et al. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003;167:1472–1477.
3. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol*. 2008;23:192–202.
4. Devarbhavi H, Singh R, Patil M, et al. Outcome and determinants of mortality in 269 patients with combination anti-tuberculosis drug-induced liver injury. *J Gastroenterol Hepatol*. 2013;28:161–167.
5. Wares DF, Singh S, Acharya AK, et al. Non-adherence to tuberculosis treatment in the eastern Tarai of Nepal. *Int J Tuberc Lung Dis*. 2003;7:327–335.
6. Van't Boveneind-Vrubleuskaya N, Daskapan A, Kosterink JG, et al. Predictors of prolonged TB treatment in a Dutch outpatient setting. *PLoS One*. 2016;11:e0166030.
7. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. *Pediatr Rep*. 2011;3:e16.
8. Akura B, Oswari H, Supriyatno B, et al. Incidence and characteristics of antituberculosis drug-induced hepatotoxicity in children: a preliminary study. *Paediatr Indones*. 2009;49:342–348.
9. World Health Organization. *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children*. 2nd ed. Geneva, Switzerland: World Health Organization; 2016.
10. Rahajoe NN, Setyanto DB, Kaswandani N, et al. *Petunjuk Teknis Manajemen TB Anak (National Guideline on the Management of Tuberculosis in Children)*. Jakarta, Indonesia: Ministry of Health of the Republic of Indonesia; 2013.
11. LiverTox: Clinical and research information on drug-induced liver injury. U.S. National Library of Medicine. Available at: https://livertox.nih.gov. Accessed September 16, 2017.
12. Centers for Disease Control and Prevention. CDC Clinical Growth Charts. 2000. Available at: https://www.cdc.gov/growthcharts/clinical_charts.htm. Accessed September 16, 2017.
13. Singanayagam A, Sridhar S, Dhariwal J, et al. A comparison between two strategies for monitoring hepatic function during antituberculous therapy. *Am J Respir Crit Care Med*. 2012;185:653–659.
14. Saukkonen JJ, Cohn DL, Jasmer RM, 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;174:935–952.
15. Tahaoğlu K, Ataç G, Sevim T, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2001;5:65–69.
16. Ohkawa K, Hashiguchi M, Ohno K, et al. Risk factors for antituberculous chemotherapy-induced hepatotoxicity in Japanese pediatric patients. *Clin Pharmacol Ther*. 2002;72:220–226.
17. Mansukhani S, Shah I. Hepatic dysfunction in children with tuberculosis on treatment with antituberculous therapy. *Ann Hepatol*. 2012;11:96–99.
18. Saukkonen J. Challenges in reintroducing tuberculosis medications after hepatotoxicity. *Clin Infect Dis*. 2010;50:840–842.
19. Makhlouf HA, Helmy A, Fawzy E, et al. A prospective study of antituberculous drug-induced hepatotoxicity in an area endemic for liver diseases. *Hepatol Int*. 2008;2:353–360.
20. Shang P, Xia Y, Liu F, et al. Incidence, clinical features and impact on anti-tuberculosis treatment of anti-tuberculosis drug induced liver injury (ATLI) in China. *PLoS One*. 2011;6:e21836.
21. Desrochers D, González-Peralta RP, McClenathan DT, et al. Isoniazid-induced severe hepatotoxicity: an infrequent but preventable cause of liver failure in children treated for latent tuberculosis infection. *Clin Med Insights Pediatr*. 2011;5:9–13.
22. Wu SS, Chao CS, Vargas JH, et al. Isoniazid-related hepatic failure in children: a survey of liver transplantation centers. *Transplantation*. 2007;84:173–179.
23. Wu S, Xia Y, Lv X, 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.
24. Kumar M, Kalita J, Tripathi A, et al. Is drug-induced hepatitis related to the severity of tuberculous meningitis? *Trans R Soc Trop Med Hyg*. 2017;111:520–526.
25. Mahmood K, Hussain A, Jairamani KL, et al. Hepatotoxicity with antituberculosis drugs : the risk factors. *Pak J Med Sci*. 2007;23:33–38.
26. Yimer G, Aderaye G, Amogne W, et al. Anti-tuberculosis therapy-induced hepatotoxicity among Ethiopian HIV-positive and negative patients. *PLoS One*. 2008;3:e1809.
27. Pande JN, Singh SP, Khilnani GC, et al. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax*. 1996;51:132–136.
28. Marzuki OA, Fauzi AR, Ayoub S, et al. Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia. *Singapore Med J*. 2008;49:688–693.
29. Lusida MI, Juniastuti, Yano Y. Current hepatitis B virus infection situation in Indonesia and its genetic diversity. *World J Gastroenterol*. 2016;22:7264–7274.