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Prophylactic antiviral treatment reduces the incidence of liver failure among patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus

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ABSTRACT

Background: China has a high prevalence of tuberculosis and hepatitis B virus infection. The purpose of this study was to determine whether HBV coinfection increases the risk of incidence of drug-induced hepatotoxicity among patients on anti-tuberculosis therapy.

Methods: This retrospective study was carried out at the First Affiliated Hospital, School of Medicine, Zhejiang University, from 2013 to 2017. All enrolled patients were confirmed HBsAg-positive for a duration of at least 6 months and coinfected with mycobacterium tuberculosis.

Results: A cohort of 90 patients was analyzed. The incidence of liver damage and liver failure was 51.11% (n = 46) and 22.22% (n = 20), respectively. By multivariate analysis, initial albumin < 35 g/l (P = 0.004, odds ratio 6.162, 95% confidence interval 1.767–21.486) was an independent risk factor for liver failure, but prophylactic antiviral treatment (P < 0.001, odds ratio 0.033, 95% confidence interval 0.007–0.154) was an independent protective factor for liver failure. Of the 90 patients, 20 developed liver failure, none of the patients with liver failure received prophylactic antiviral therapy, and 6 of those patients died of liver failure.

Conclusions: Prophylactic antiviral treatment reduces the incidence of liver failure in patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus; therefore, it is recommended that prophylactic antiviral treatment be administered while receiving anti-tuberculosis treatment in patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus.

1. Background

Tuberculosis (TB) is a serious public health problem in China, especially in the western region of China. In 2014, there were 1,300,000 new cases and 38,000 deaths from TB in China, which represented the third-highest prevalence of TB worldwide (Glaziou et al., 2018). Chronic hepatitis B is also a major health problem in China. The universal vaccination program since 1992 has changed the epidemiology of hepatitis B virus infection in China from highly to moderately endemic. There were still an estimated 93 million chronic HBV infections and a prevalence of 7.8% hepatitis B virus surface antigen (HBsAg)-positive people (Hou et al., 2017).

No new anti-tuberculosis drug has been validated as effective in recent years. Although the use of a multidrug regimen for the treatment of TB with a combination of isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) is a highly effective strategy, liver toxicity is a common side effect of anti-tuberculosis drugs, even leading to liver failure (Annon., 2019). Globally, the prevalence of HBV infection among patients with TB has not been extensively investigated, and very limited data on rates of HBV coinfection among patients with TB exist. Some previous studies reported that the incidence of liver dysfunction was significantly higher in HBV carriers given anti-TB drugs (Wong et al., 2000; Pan et al., 2005), especially patients with high viral loads (Zhu et al., 2017; Wang et al., 2011). Some previous studies

Abbreviations: HBV, hepatitis B virus; ULN, upper limit of normal; TBil, total bilirubin; PTA, prothrombin activity; HBsAg, hepatitis B virus surface antigen; INH, isoniazid; RIF, rifampicin; EMB, ethambutol; PZA, pyrazinamide; DIH, drug-induced hepatotoxicity; HIV, human immunodeficiency virus; CI, confidence interval; PT, prothrombin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; UA, uric acid; TB, total bilirubin; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; Fib, fibrinogen; TBA, total bile acid

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reported that HBV infection had no significant effect on the incidence of drug-induced hepatotoxicity (DIH) (Liu et al., 2014; Nooredinvand et al., 2015; Kim et al., 2016). None of the studies published to date have assessed whether prophylactic antiviral treatment decreases the risk of anti-tuberculosis DIH among patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus. We report a retrospective study to compare the incidence and severity of anti-TB drugs related to DIH in patients with prophylactic antiviral treatment and in patients without prophylactic antiviral treatment.

2. Methods

2.1. Study design

We retrospectively enrolled patients diagnosed with TB who were receiving anti-tuberculosis agents at the First Affiliated Hospital of the Zhejiang University School of Medicine (Hangzhou, China) from January 2013 to December 2017. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University. All patients enrolled were HBsAg-positive for a duration of at least 6 months and coinfected with mycobacterium tuberculosis. Patients coinfected with and hepatitis delta virus, hepatitis A virus, hepatitis E virus, hepatitis C virus, or human immunodeficiency virus (HIV) were excluded. Patients with congestive heart failure, autoimmune hepatitis, alcohol abuse, diabetes mellitus, chronic kidney disease, liver cirrhosis or hepatic malignancy were also excluded. Patients with abnormal baseline liver function test results, those who were lost to follow-up, transferred to other institutions, had stopped anti-TB treatment because an alternative diagnosis was made, and whose death was not attributable to DIH were excluded.

2.2. Definitions of DIH, mild hepatitis flare, moderate hepatitis flare, severe hepatitis flare and hepatic failure

The criteria used to define DIH were based on previous study recommendations (Annon., 2019; Zhu et al., 2017; Yew and Leung, 2006). DIH was confirmed in a patient if the liver transaminase level exceeded 120 IU/L with symptoms of acute hepatitis or if it exceeded 200 IU/L with or without symptoms of acute hepatitis while the anti-TB drug treatment was stopped, and if the liver transaminase level increased to 120 IU/L. Increased serum transaminase levels, which were 3 or 5 times above the upper limit of normal (ULN), were defined as mild and moderate hepatitis flares, respectively. Severe hepatitis flares were defined when ALT levels were elevated to 10 times the ULN (> 400 U/L) (Wang et al., 2011). Liver failure was identified when total bilirubin was elevated more than 10 times the ULN (> 171 μmol/L) with decreased (< 40%) PTA levels, with or without hepatic encephalopathy (Liver and Artificial Liver Group CSoIDCMA, 2013).

2.3. Statistical analysis

Statistical analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean ± SD and compared between the groups using Student's *t*-test Categorical variables were compared by using the χ^2 test. The odds ratio (OR), 95% confidence interval (CI), and multiple logistic regression were used to assess the risk factors associated with the development of hepatitis during treatment. Potential factors associated with different levels of hepatotoxicity on baseline among the groups of normal, mild to moderate/hepatitis flare, and severe hepatitis flare/hepatic failure were analyzed by one-way analysis of variance (ANOVA). Product limit survival estimates were created using Kaplan-Meier survival curves, and the log-rank test was used to evaluate significant differences between patients with liver failure who received prophylactic antiviral therapy and no prophylactic antiviral therapy. p values less than 0.05 were considered significant.

Table 1
Summary of clinical and laboratory characteristics.

Variables	Mean ± SD	Minimum	Maximum
Age (years)	42.52 ± 14.53	16	83
ALT	213.62 ± 317.43	4	1549
AST	180.04 ± 296.77	14	1323
TB	105.88 ± 165.34	4	589
GGT	73.92 ± 63.02	9	372
ALP	96.54 ± 39.52	23	209
Alb	38.21 ± 7.37	23.5	53.1
Glo	27.38 ± 5.64	13.2	40.2
TBA	71.97 ± 102.78	2	441
UA	285.61 ± 158.58	60	925
Cr	66.28 ± 23.96	23	180
Fib	2.67 ± 1.39	0.5	7.6
PT	15.27 ± 5.67	10.2	37
WBC	5.90 ± 2.75	2.1	19
Hb	131.94 ± 21.7	76	171
PLT	183.82 ± 89.75	26	440
ESR	15.63 ± 19.78	1	87
HBVDNA(log10 IU/mL)	4.56 ± 2.41	1.30	9.71
HBsAg (log10 IU/mL)	3.07 ± 1.08	0.29	5.10
HBeAg	51.15 ± 113.36	0	430.18
Time of liver damage	90.86 ± 14.53	7	227

3. Results

3.1. Demographic data

We enrolled 90 patients treated with anti-tuberculosis agents; all of the patients were positive for HBsAg, and their demographics are presented in Table 1. The mean age was 42.52 ± 14.53 years old (range, 16–83) with 68 (75.56%) males and 22 (24.44%) females, and 12 (13.33%) and 78 (86.67%) of them were older than 60 years old and under 60 years old, respectively. Forty patients (44.44%) were e antigen-positive, and 50 (55.55%) were e antigen-negative. Thirty-seven patients (41.11%) had high hepatitis B surface antigen (HBsAg ≥ 1500 IU/ml), and 53 patients (58.89%) had low HBsAg (HBsAg < 1500 IU/ml). Thirty-nine (43.33%) patients had high viral loads (HBVDAN > 10^5 IU/ml). Routine biochemical tests showed that 36 (40.0%) patients in this cohort presented with hypoproteinemia, while the remaining 54 patients (60.0%) did not. Forty-four (48.89%) patients had received prophylactic antiviral therapy, and 46 (51.11%) had not received prophylactic antiviral therapy. Of the 44 patients who received prophylactic antiviral therapy, 15 received 100 mg of lamivudine orally once daily, and 29 received 0.5 mg of entecavir orally once daily. Detailed data are summarized in Table 1.

3.2. Incident hepatotoxicity and risk factors for hepatotoxicity

All factors were compared among the three defined levels of hepatotoxicity as shown in Table 2. Hepatotoxicity (definition of liver dysfunction as previously mentioned) during anti-TB treatment occurred in 46 of 90 patients (51.11%). Five patients developed a mild hepatitis flare (5.56%), 8 patients developed a moderate hepatitis flare (8.89%), 13 patients developed a severe hepatitis flare (14.44%), and 20 (22.22%) patients developed liver failure. Interestingly, age, gender, HBeAb status, and high HBsAg did not significantly correlate with the severity of the hepatitis flare. We found that higher viral loads, preventive antiviral treatment and albumin levels were significantly related to the severity of liver dysfunction ($P < 0.05$). Detailed data are summarized in Table 2. In addition, the ratio of patients who received prophylactic antiviral treatment was significantly lower in the severe liver damage or liver failure groups than in the normal liver function group.

By comparing clinical test results among the three groups, we found that age was not significantly correlated with the severity of the

Table 2
Potential factors associated with different levels of hepatotoxicity on the baseline.

Variables n (%)	Total (n = 90)	Normal (n = 44)	Mild to moderate hepatitis flare (n = 13)	Severe hepatitis flare hepatic failure (n = 33)	P
Age					0.293
< 60 years old	78	36	11	31	
≥60 years old	12	8	2	2	
Gender					0.440
Male	68	34	8	26	
Female	22	10	5	7	
HBeAg					
Positive	40	21	6	13	0.760
Negative	50	23	7	20	
HBVDNA					
$\geq 10^5$IU/ml	39	12	9	18	0.007
$< 10^5$IU/ml	51	32	4	15	
HBsAg					
≥1500IU/ml	37	17	4	16	0.490
< 1500IU/ml	53	27	9	17	
ALB					
≥35 g/l	54	34	8	12	0.001
< 35 g/l	36	10	5	21	
Anti-virus					
Yes	44	37	4	3	< 0.001
No	46	7	9	30	

hepatitis flare. PT was significantly more prolonged in the severe group (severe hepatitis flare or liver failure) than in the group with mild to moderate hepatitis flares. On the other hand, there was a significant association between serological ALB levels and the degree of liver damage; the concentration of albumin in the severe hepatitis flare and liver failure groups was lower than that in the mild and moderate hepatitis flare groups. In addition, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid (UA), total bilirubin (TB), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) and fibrinogen (Fib) levels could be used to predict the severity of hepatotoxicity. Detailed data are summarized in Table 3.

3.3. Logistic regression

Based on previous research and the aforementioned results, possible risk factors, including advanced age, gender, positive HBeAg, high levels of HBsAg, high HBV-DNA loads, prophylactic antiviral treatment, and hypoproteinemia, were entered into a logistic regression analysis. By multivariate analysis, initial albumin < 35 g/l (P = 0.004, odds ratio 6.162, 95% confidence interval 1.767–21.486) was an independent risk factors for liver failure, but prophylactic antiviral treatment (P < 0.001, odds ratio 0.033, 95% confidence interval 0.007 to 0.154) was an independent protective factor for liver failure (Table 4).

Table 4
Variables associated with development of Severe hepatitis flare/hepatic failure during antituberculous therapy by multiple logistic regression.

Risk factors	OR	95% CI	*p*
Initial albumin < 35 g/L	6.162	1.767–21.486	0.004
HBVDNA ≥ 10^5IU/ml	1.289	0.331–5.030	0.714
Prophylactic antiviral treatment	0.033	0.007–0.154	< 0.001
Age ≥ 60 years old	4.224	0.525–33.975	0.176
HBsAg ≥ 1500IU/ml	1.292	0.303–5.507	0.729
Gender is male	2.889	0.673–12.406	0.154
HBeAg(+)	1.324	0.335–5.228	0.689

OR = odds ratio; CI = confidence interval; HBsAg= Hepatitis B surface antigen; HBeAg = hepatitis B e antigen.

3.4. Mortality

Of the 90 patients, 20 developed liver failure, none of the patients with liver failure received prophylactic antiviral therapy, and 6 of these patients died of liver failure. Patients who received prophylactic antiviral therapy did not develop liver failure, and no deaths were found by the end of anti-tuberculosis treatment. Compared to patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus who did not receive prophylactic antiviral treatment, Kaplan-Meier survival curves showed a higher survival rate among the coinfected patients who had received prophylactic antiviral treatment (p = 0.0138) (Fig. 1).

4. Discussion

The use of multidrug regimens for anti-TB treatment based on the combination of INH, RIF, EMB, and PZA has proven to be a highly effective therapy. However, DIH associated with first-line anti-TB drugs is a common side effect and often necessitates the modification or interruption of anti-TB treatment (Fernandez-Villar et al., 2004). WAI-MAN

Table 3
Clinical test results correlated with levels of hepatotoxicity.

Variables	Normal	Mild to moderate hepatitis flare	Severe hepatitis flare/ hepatic failure	*P*
Age (years)	42.57 ± 17.07	41.54 ± 13.41	42.85 ± 11.31	0.963
ALT (U/L)	26.21 ± 17.15	173.61 ± 112.18	479.27 ± 391.69	< 0.001
AST (U/L)	26.09 ± 10.76	127.59 ± 89.49	405.97 ± 394.28	< 0.001
TB	11.93 ± 7.70	13.85 ± 10.12	267.41 ± 182.86	< 0.001
GGT	43.68 ± 35.48	85.54 ± 93.62	109.67 ± 58.64	< 0.001
ALP	78.55 ± 30.32	102.92 ± 41.37	118.03 ± 39.11	< 0.001
Alb	40.98 ± 7.91	37.95 ± 4.39	34.64 ± 6.00	0.001
Glob	26.85 ± 4.12	31.09 ± 6.22	26.62 ± 6.68	0.035
TBA	8.25 ± 8.73	32.69 ± 74.53	172.39 ± 102.89	< 0.001
UA	355.77 ± 165.13	309.31 ± 126.63	182.73 ± 96.82	< 0.001
Cr	72.09 ± 25.59	64.23 ± 19.54	59.33 ± 21.82	0.064
Fib	4.11 ± 2.91	3.81 ± 3.39	1.75 ± 0.75	< 0.001
PT	12.36 ± 3.73	11.85 ± 2.16	19.73 ± 6.42	< 0.001
WBC	6.00 ± 2.51	5.23 ± 2.12	6.03 ± 3.28	0.642
Hb	135.89 ± 22.80	128.92 ± 16.09	127.88 ± 21.72	0.241
PLT	216.89 ± 94.93	204.77 ± 75.35	131.48 ± 60.49	< 0.001
ESR	17.00 ± 17.54	30.46 ± 32.21	8.00 ± 11.44	0.001
HBsAg (log10 IU/mL)	3.00 ± 1.10	2.95 ± 1.12	3.21 ± 1.58	0.665
HBV DNA (log10 IU/mL)	3.57 ± 2.14	5.94 ± 2.09	5.33 ± 2.37	< 0.001

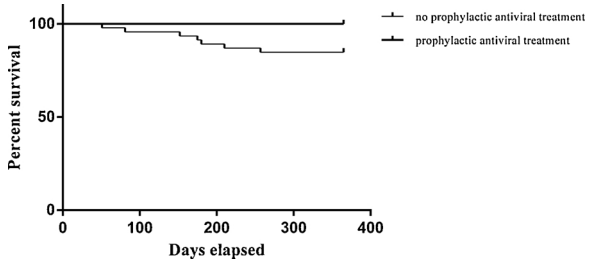

Fig. 1. Survival comparison of patients with and without Prophylactic antiviral treatment, the difference in survival between patients with Prophylactic antiviral treatment and without Prophylactic antiviral treatment was statistically significant (P = 0.0138).

WONG et al showed that hepatitis B carriers given anti-TB treatment had a higher proportion of hepatic dysfunction compared to noncarriers (34.9% vs. 9.4%, P < 0.001) (Wong et al., 2000). Many other studies show that anti-TB drug-induced hepatotoxicity was higher in TB patients with chronic HBV coinfection compared to uninfected subjects (Pan et al., 2005; Zhu et al., 2017; Wang et al., 2011; Chen et al., 2018). Hepatitis B virus infection is a high risk factor for DIH. Can preventive antiviral therapy reduce the incidence of DIH? This study examined the rates of liver failure in 90 patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus. We found a higher incidence of liver failure and risk of death in patients without prophylactic antiviral treatment than in those with prophylactic antiviral treatment. Prophylactic antiviral treatment was an independent protective factor for liver failure.

Liver failure has very high mortality, and the 90-day mortality was 63% (Garg et al., 2012). Compared with patients in the TB group, patients in the TB-HBV group who did not receive anti-HBV therapy before anti-TB treatment were more susceptible to Grade-4 severity of DILI (36.2% vs. 7.7%, P = 0.005), liver failure (67.2% vs. 38.5%, P = 0.013) and poor outcomes (37.9% vs. 7.7%, P = 0.005) (Chen et al., 2018). The study by Chun-hui ZHU et al showed that patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus experience a high mortality rate; the prognosis of these patients is usually very poor, and 10 of 22 patients suffering from liver failure died during treatment, despite prompt and reasonable treatment (Zhu et al., 2017). In our research, 20 patients developed liver failure, and 6 of those patients died of liver failure. Patients on anti-TB therapy with chronic HBV coinfection are more susceptible to developing liver failure, and prophylactic antiviral treatment should be considered in those with high viral levels before anti-TB treatment.

Previous studies have reported that DIH usually occurred within the initial 2 months of therapy (Sun et al., 2009; Girling, 1982). Our study also showed that most mild and moderate hepatitis flares occurred within the initial 2 months of therapy. However, we found that most (18/20) liver failure occurred later in patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus. One possible explanation is a flare-up of the chronic hepatitis virus. Therefore, we found that patients who received prophylactic antiviral therapy did not develop liver failure.

We did not find significant associations between the severity of liver injury and age, gender, HBeAg positivity, or HBsAg level at baseline. However, high HBV-DNA loads (more than 10^5 IU/ml) were significantly associated with the severity of liver injury. Furthermore, prophylactic antiviral treatment reduced the incidence of liver failure. The results are consistent with other reports (Zhu et al., 2017; Sun et al., 2009). In our study, hypoalbuminemia at baseline was identified as an independent risk factor for the development of liver failure in HBV-infected patients during anti-tuberculosis treatment. This finding agrees with those reported by Singla, R et al and Zhu C. H. et al. (Zhu et al., 2017; Singla et al., 2010). We found that the levels of ALT, AST, TB, GGT, ALP, TBA, and PT correlated with the severity of liver damage. Monitoring these indicator levels was necessary to monitor hepatotoxicity. Once these indicators are found to be abnormal, the frequency of clinical and laboratory monitoring should be increased, perhaps every 2 weeks or when clinically indicated, to decide if further regimen adjustment is needed (Blumberg et al., 2003; Tostmann et al., 2008).

There were some limitations to our study. First, because this was a retrospective study, some patients' liver function at the very beginning of anti-tuberculosis treatment could not be evaluated. A small number of patients were transferred to our hospital for treatment of liver failure due to lack of preventive antiviral therapy in the other hospital, which may lead to a high incidence of liver failure in the group that did not receive preventive antiviral therapy. Second, due to the lack of a pathological examination, we could not determine the exact cause of liver damage, whether it was drug-induced or caused by hepatitis B virus relapse, which can only be determined by rechallenge with anti-tuberculosis therapy. Third, our research is a single-center study and had a limited number of cases enrolled, which makes it more difficult to extend our results to a larger population.

5. Conclusion

Prophylactic antiviral treatment reduces the incidence of liver failure in patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus; therefore, it is recommended that prophylactic antiviral treatment be administered while receiving anti-tuberculosis treatment in patients coinfected with *Mycobacterium tuberculosis* and hepatitis B virus, especially the patients had high viral loads (HBVDAN > 10^5 IU/ml).

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of First Affiliated Hospital, School of Medicine, Zhejiang University.

Consent to publish

Not applicable.

Availability of data and materials

The data and materials in the current study are available from the corresponding author on reasonable request.

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Author contributions

Jiangshan Lian and Yingfeng Lu contributed equally to this work; Jiangshan Lian, Yingfeng Lu and Yueying Liu performed the majority of experiments; Xiaoxiao Wang, Yimin Zhang and Hongyu Jia provided analytical tools and revised the manuscript; Yida Yang designed the study; Jiangshan Lian and Yang Yida Yang wrote the manuscript.

Declaration of competing interest

The authors declare that they have no potential conflicts of interest.

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