Prevalence and risk factors of anti-tuberculosis drug-induced hepatitis in Malaysia

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ABSTRACT

Introduction: Tuberculosis (TB) affects one-third of the world's population. Anti-TB drugs with isoniazid, rifampicin and pyrazinamide are very effective but they can cause hepatotoxicity. Many risk factors have been recognised. Data on prevalence of anti-TB drug-induced hepatitis as well as the contributing risk factors are scarce in Malaysia. This observational case control study was designed to look at the prevalence and the risk factors of drug-induced hepatitis in our population.

Methods: We retrospectively examined all the case notes of anti-TB drug-induced hepatitis over a 30-month period from January 2003 to June 2005. They were compared with controls selected by simple random sampling. Both groups were compared in terms of demographical data and risk factors, such as age, gender, body mass index, hepatitis B carrier, human immunodeficiency virus (HIV) infection, sites of TB, and pretreatment liver biochemistries (serum albumin, globulin, aspartate aminotransferase, alanine aminotransferase and bilirubin). Data was evaluated by chi square, independent t-test (univariate) and binary logistic regression analysis (multivariate).

Results: Out of 473 TB patients, 46 developed hepatitis and 138 were selected as controls. The prevalence of drug-induced hepatitis was 9.7 percent. On univariate analysis, HIV infection (p-value is 0.005), extrapulmonary tuberculosis (p-value is 0.008), lower serum albumin (p-value is 0.023) and higher serum globulin (p-value is 0.025) were significant risk factors. On binary logistic regression, only HIV infection (p-value is 0.018) and extrapulmonary TB (p-value is 0.017) were significant.

Conclusion: The prevalence of hepatitis was 9.7 percent. The presence of HIV infection and extrapulmonary TB were significant risk factors for the development of hepatitis.

Keywords: anti-tuberculosis drugs, drug-induced hepatitis, extrapulmonary tuberculosis, hepatoxicity, isoniazid, pyrazinamide, rifampin, toxic hepatitis

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INTRODUCTION

Tuberculosis (TB) is a global pandemic and the incidence is rising.[1] The largest number of cases occurs in the Southeast Asia region, which accounts for about a third of the global prevalence.[2] In Malaysia, ranked 46th in total number of TB cases, 14,908 new cases were reported in 1999 with the majority of cases occurring in the economically-productive age of 15–50 years.[3] Per 100,000 population, our incidence is 47 per year, prevalence 136 cases and mortality rate associated with TB is estimated at 17 cases per year.[2] Chemotherapeutic agents using rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin are highly effective, but drug-induced hepatotoxicity is a real problem. Occasionally, this side effect is predictable and dose dependent, but for most, it is idiosyncratic, dependent on parameters such as drug dosage, age, gender, and body mass index (BMI).[4] Concurrent use of certain food, drugs, pregnancy as well as underlying renal or liver disease also play a significant role.

The occurrence of anti-TB hepatotoxicity is variable. The incidence is higher in the developing countries with rates ranging from 8% to 39%, compared to developed countries at 3%–4%, despite similar regimens used.[5-8] As a specific example, a higher risk of 11.5% has been reported in Indian patients, compared to 4.3% in published studies from the developed countries.[5,9,10] One recent study from Singapore reported an incidence of 5.3%.[11] A number of risk factors have been implicated. These include older age, female gender, poor nutritional status, high alcohol intake, pre-existing liver disease, hepatitis B carriage, increased prevalence of viral hepatitis in developing countries, hypoalbuminaemia and advanced TB.[12-16] Inappropriate use of drugs, acetylator status, and recently, immunogenetic factor, have also been implicated.[17,18] Infections with hepatitis C virus and human immunodeficiency virus (HIV) have also been said

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to increase the risk.[19]

In one prospective hospital-based survey in Malaysia, the authors had found that those who developed anti-TB drug-induced hepatitis had lower mean BMI, lower serum albumin and higher serum globulin.[20] Among other risk factors studied, only chronic hepatitis B carrier status was found to be more prevalent among the cases. To the best of our knowledge, there is no other known published data on the prevalence of anti-TB drug-induced hepatitis in Malaysia. Similarly, there is no data on the significance of multiple risk factors which may contribute to the development of anti-TB drug-induced hepatitis in this part of the region. This study is designed to examine these issues.

METHODS

This was a retrospective study carried out at Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia. HUSM is a tertiary care teaching hospital for the medical faculty of Universiti Sains Malaysia. All the case notes of patients with TB registered at HUSM Chest Clinic from January 1, 2003 to June 30, 2005 (30 months) were analysed for cases with anti-TB drug-induced hepatitis. Malaysia has a TB control programme. Under the programme, patients suspected to have TB will undergo a series of tests. These tests include serial sputum direct smear (three samples), full blood counts (FBC), erythrocyte sedimentation rate (ESR), urea and electrolytes (U+E), baseline liver function tests (LFT) and HIV screening. Once the diagnosis is confirmed or the decision to treat has been made, TB treatment is commenced after reviewing the blood results. The first line anti-TB treatment regimens were either a combination of streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ), or a combination of ethambuthol, isoniazid, rifampicin and pyrazinamide (EHRZ). Any abnormality noted would necessitate adjustment to the treatment regime or further tests being done to ascertain the cause. In the case of hepatitis, viral serology screen (Hepatitis A, B and C) and ultrasonography were performed. Directly-observed therapy short course (DOTS) was implemented almost universally, unless this was not physically or socially possible. The usual hindrance was the distance and lack of transport to bring the patient to the nearest chest clinic.

All TB patients were reviewed at two weeks upon treatment and thereafter every two months until the treatment was completed. During the review, inquiries were made about compliance, drug side effects, tolerability as well as any worsening symptoms to indicate other diagnoses. If drug-induced hepatitis was suspected, a repeat LFT was performed. However, at the study centre, repeat LFTs were done routinely at one to two weeks after the commencement of therapy in most of the patients though they were asymptomatic. Inquiries were also made into the social and financial constraints to the family as the cost of DOTS might be a burden, though some form of funding can usually be initiated. The duration of treatment varied
from a minimum of six months to one year in some cases.

All cases of hepatitis fulfilling the criteria outlined below were treated with treatment cessation. Biweekly LFTs guided the doctor on the progress of the hepatitis. Once the LFT results had returned to normal, drug challenge was commenced until an acceptable treatment combination was reached. Most patients, however, could be safely restarted on the previous regimen consisting of the primary drugs. Inclusion criteria were:[19]

1. Normal LFT prior to starting anti-TB drugs regimen.
2. No history of alcohol abuse or other substances abuse for at least ten days prior to starting anti-TB medications.
3. Drugs were given in standard doses (isoniazid: 5–8 mg/kg/day; rifampicin: 10–15 mg/kg/day; pyrazinamide: 20–40 mg/kg/day),[3] alone or in combination for at least five days prior to the development of hepatitis.
4. Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) increased to ≥ 120 IU/L (normal ≤ 40 IU/L) and/or an increase in total bilirubin to > 1.5 mg/dL (25 µmol/L)(normal < 1.5 mg/dL or < 25 µmol/L), at least five days after starting anti-TB drugs with no other apparent causes of abnormal LFT.

Exclusion criteria were:

1. Patients with hepatitis meeting the inclusion criteria above prior to commencement of anti-TB medications.
2. Serological evidence of an acute infection with hepatitis B or C in those diagnosed to have hepatitis.
3. Receiving a higher dosage of anti-TB drugs than the recommended dosage according to body weight.
4. Inadequate medical records to allow complete analysis.
5. Receiving other potentially hepatotoxic medications concurrent with the anti-TB treatment.

The data collected in the study was analysed by using the Statistical Package for Social Sciences version 12.0.1 (SPSS Inc, Chicago, IL, USA). Categorical variables, such as patients' gender, hepatitis B virus carrier status, HIV infection, sites of TB and treatment regimens, were

Table I. Baseline characteristics of cases and controls.

Characteristics	No. cases (%) (n = 46)	No. controls (%) (n = 138)
Age (years)		
≤ 35	14 (30)	41 (30)
> 35	32 (70)	97 (70)
Gender		
Male	32 (70)	87 (63)
Female	14 (30)	51 (37)
Ethnic group		
Malay	46 (100)	127 (92)
Chinese	0	7 (5)
Others	0	4 (3)
Medical illness		
Diabetes mellitus		
Yes	4 (9)	32 (23)
No	42 (91)	106 (77)
Hepatitis B carrier		
Yes	3 (7)	2 (1)
No	43 (93)	136 (99)
HIV		
Yes	9 (20)	8 (6)
No	37 (80)	130 (94)
Sites of tuberculosis		
Pulmonary	22 (48)	96 (70)
Extrapulmonary	24 (52)	38 (27)
Mixed	0	4 (3)
Treatment regimens		
SHRZ	25 (54)	87 (63)
EHRZ	14 (30)	41 (30)
HRZ	7 (15)	10 (7)

HIV: human immunodeficiency virus; S:streptomycin; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol.

Table II. Sites of tuberculosis.

Sites	No. cases (%) (n = 46)	No. controls (%) (n = 138)
Pulmonary TB	22 (48)	96 (70)
Extrapulmonary TB*	24 (52)	38 (27)
Bones and joints	5 (21)	11 (29)
Lymph nodes	6 (25)	9 (24)
Meningitis	6 (25)	5 (13)
Miliary	3 (13)	3 (8)
Gastrointestinal	1 (4)	3 (8)
Pleural	1 (4)	2 (5)
Genitourinary	1 (4)	2 (5)
Ocular	1 (4)	1 (3)
Others	0	2 (5)
Pulmonary and extrapulmonary TB	0	4 (3)

*The percentages of the various types of extrapulmonary TB were percentages over the total number of extrapulmonary cases in both groups, 24 and 38, respectively.

expressed in frequency and percentage, whereas numerical variables such as patients' age, BMI, serum albumin, serum globulin, serum ALT, serum AST and serum bilirubin were expressed in means and standard deviation. The various risk factors in the study population were analysed with independent *t*-test and chi-square test to evaluate their association with the development of anti-TB drug-induced hepatitis. The independent variables were then evaluated with binary logistic regression to identify the factors that were significant in the development of hepatitis. A p-value < 0.05 was considered to be statistically significant.

RESULTS

A total of 473 patients were registered at the Chest Clinic of HUSM during the study period. 58 patients had evidence of hepatitis, but only 46 were eligible and 12 were excluded. Those excluded were four who had active hepatitis C or hepatitis B, three with non-specific pretreatment hepatitis, three with incomplete medical records and another two defaulted follow-up. History of alcohol intake was not significant in both the cases and controls. All patients who had admitted to consuming alcohol were ex-drinkers with an intake of less than eight units per week.

Controls (138) were selected using the simple random sampling method, producing a ratio of one case to three controls. The baseline characteristics of all patients included in the study are summarised in Table I. The mean age for cases and controls were 44.1 and 47.0 years, respectively, and ranged from 17 to 87 years of age. The majority of the patients in both cases and controls were in the older age group (> 35 years). There were 32 males (70%) among cases and 87 males (63%) in the control group, and the vast majority of the studied population (94%) were Malays. There were four diabetic patients (9%) among the cases, compared to 32 in the control group (23%).

The majority of all the patients (64%) had pulmonary TB (PTB). Another 62 (34%) had extrapulmonary TB (EPTB), while the remaining four had both. The number of EPTB was slightly higher in the cases group (52%), whereas in control group, the number of PTB was much higher (70%). Most patients received the SHRZ regimen (54% in cases and 63% in controls). Others received EHRZ (30% in both groups) and HRZ (15% and 7%, respectively) regimens. The three main organs involved in EPTB were bones and joints (21% of cases and 29% of controls), lymph nodes (25% cases and 24% controls), and meninges (25% cases and 13% controls). Others include miliary, gastrointestinal, pleural, genitourinary tract and ocular organs (Table II). From the study, the prevalence of anti-TB drug-induced hepatitis was 9.7%. There was no difference between cases and controls in the older age group (> 35 years), gender and hepatitis B carrier status. There were, however, more patients with HIV infection and EPTB among cases, compared to controls (Table III). When comparing baseline characteristics, lower pretreatment albumin ($p = 0.023$) and higher globulin ($p = 0.025$) levels were significant risk factors.

For multivariable analysis, several variables were included to determine the significance of the risk factors (Table IV). By univariate analysis, HIV infection ($p = 0.005$), EPTB ($p = 0.008$), lower albumin ($p = 0.023$) and higher globulin ($p = 0.025$) were significant. To determine

Table III. Baseline variables in cases and controls.

Variables	No. cases (%) (n = 46)	No. controls (%) (n = 138)	p-value
Age > 35 years	32 (70)	97 (70)	0.926
Female gender	14 (30)	51 (37)	0.423
Hepatitis B carrier	3 (7)	2 (1)	0.101*
HIV infection	9 (20)	8 (6)	0.005
Extrapulmonary TB	24 (52)	42 (30)	0.008

HIV: human immunodeficiency virus
* Fisher's exact test

Table IV. Risk factors included in the multivariable analysis.

Variables	p-value
Age > 35 years	0.926
Female gender	0.423
Hepatitis B virus carrier	0.101*
HIV infection	0.005
Extrapulmonary TB	0.008
Mean BMI	0.589
Mean serum albumin	0.023
Mean serum globulin	0.025
Mean serum ALT	0.360
Mean serum AST	0.197
Mean serum bilirubin	0.607

HIV: human immunodeficiency virus; BMI: body mass index; ALT: alanine aminotransferase; AST:aspartate aminotransferase
* Fisher's exact test.

the independent risk factors for the development of anti-TB drug-induced hepatitis, binary logistic regression analysis was used. All variables of risk factors with p-value < 0.05 were included in the final analysis by using three methods, namely: Manual Backward Elimination method, Backward Stepwise-Likelihood Ratio method and Forward Stepwise-Likelihood Ratio method. Based on the results obtained, the most biologically plausible outcome was selected, i.e. results from the Backward Stepwise-Likelihood Ratio method. The analysis showed that the presence of EPTB (p = 0.017) and underlying HIV infection (p = 0.018) were independent risk factors in the development of anti-TB drug-induced hepatitis, with percentage correct of 76.6% (Table V).

DISCUSSION

The prevalence of anti-TB drug-induced hepatitis found in this study was 9.7%, comparable with those reported in other Asian countries, ranging from 8% to 39%.[5,6] This is higher compared to those of developed countries, around 3%–4%.[7] The reasons for this are unclear. One possible explanation is the higher prevalence of viral hepatitis in developing countries.[5,6,15] Since this study did not include patients with active hepatitis B and C, the role of viral hepatitis in the development of anti-TB drug-induced hepatitis could not be ascertained. We however showed that there was no significant relationship between the hepatitis B carrier status and the development of anti-TB drug-induced hepatitis (p = 0.101), but the number of hepatitis B carriers in our study was very small (five patients). Further studies are needed to examine other possible risk factors for the development of anti-TB drug-induced hepatitis, such as the role of genetic factors as well as acetylator status in our local population.

Underlying HIV infection (p = 0.005), EPTB (p = 0.008), lower serum albumin (p = 0.023) and higher serum globulin (p = 0.025) were found to be associated with a higher risk of developing anti-TB drug-induced hepatitis on univariate analysis. Analysis with multivariate logistic regression however found only underlying HIV infection (p = 0.018) and EPTB (p = 0.017) to be significant in the development of anti-TB drug-induced hepatitis. Further larger-scale local studies are needed to validate these findings in the development of anti-TB drug-induced hepatitis in our populations. In our study, the mean BMI for both cases and controls were comparable (20.9 and 20.8 kg/m^2, respectively) and therefore not significant (p = 0.589). However, we found that the cases had a significantly lower level of serum albumin (p = 0.023) and a higher level of serum globulin (p = 0.025), similar to findings in one local study.[20] These were also consistent with other studies which found that patients with pretreatment hypoalbuminaemia had a twofold or threefold higher risk of developing anti-TB drug-induced hepatitis.[18,21] However, in our study, both findings were not significant on multivariate logistic regression analysis.

We found that HIV positivity was a significant independent risk factor for developing anti-TB drug-induced hepatitis by multivariate logistic regression analysis (p = 0.018), similar to other studies.[19,22] This might be related to an underlying viral replication or the immunocompromised state in patients with HIV infection. There was also an increasing prevalence of co-infection of HIV with either hepatitis B virus or hepatitis C virus, which might have contributed to the development of drug-induced hepatitis.[23] Apart from that, HIV patients tend to suffer from some degree of malnutrition, including hypoalbuminaemia. This in turn might also contribute to

Table V. Association between risk factors and anti-tuberculosis drug-induced hepatitis using binary logistic regression analysis.

Variables	OR	95% CI of OR		p-value	Percentage correct	Hosmer and Lemeshow test
		Lower	Upper			χ^2 (p-value)
Extrapulmonary TB						
Positive	2.33	1.16	4.67	0.017		
Negative	1					
HIV						
Positive	3.54	1.25	10.05	0.018	76.6	6.368 (0.606)
Negative	1					
Constant	0.20			0.000		

OR: odds ratio; CI: confidence interval; HIV: human immunodeficiency virus

the development of anti-TB drug-induced hepatitis. HIV patients might also have a more severe and advanced TB infection, depending upon the stage of the HIV disease, in itself an independent risk factor for the development of anti-TB drug-induced hepatitis.[13,16,18]

We also found that EPTB was a significant risk factor by multivariate logistic regression analysis (p = 0.017). This finding is somewhat interesting, since there are not many published reports highlighting this apart from a few reports in the paediatric age group patients.[24] The reason for this is unclear, but could be related to the severity and extent of the underlying disease. In our study, it could be due to the presence of HIV infection since most of the patients with EPTB had an underlying HIV infection.

For the purpose of analysis, age was divided into two categories, younger age group (≤ 35 years of age) and older age group (> 35 years old) based on previous studies in which 35 years of age was used as a cut-off point.[13,19,25] We did not find significant association between age and the risk of developing anti-TB drug-induced hepatitis. The mean age for the cases and controls were 44.1 and 47.0 years, respectively (p = 0.319). Patients in the older age group did not have a higher risk of developing drug-induced hepatitis compared to patients in the younger age group (p = 0.926). Previous data had shown that the older patients (mean age of 70 years) needed dosage modification compared to the younger patients (mean age 41 years), and as a group, the risk of hepatotoxicity was higher.[11,26,27] We did not show any significant role of advanced age in the development of anti-TB drug-induced hepatitis. Our sample population was mostly younger patients with underlying HIV.

In our study, gender was not significant (p = 0.423) in hepatotoxicity, although other studies had indicated that the female gender was a risk factor.[13,26] This is probably because almost two-thirds (64.7%) of our study population were males. Future studies must ensure an equal gender distribution in order to look at gender as a risk factor in our local population. We found more hepatitis B virus carriers among the cases group (6.5%) as compared to the controls (1.4%), but this was not significant (p = 0.101), consistent with several earlier studies.[27,28] Newer studies however found that hepatotoxicity developed more frequently in HBsAg carriers than in non-carriers.[25] It should be noted that up to 15%–20% of HBsAg carriers in the inactive state were found to have exacerbations of hepatitis with or without HBeAg seroconversion. We also found that pretreatment ALT (p = 0.360), AST (p = 0.197) and serum bilirubin (p = 0.607) had no significant difference between the cases and controls. A few limitations in this study included incomplete documentation in some cases, which were therefore excluded from the analysis. Secondly, we did not test for the phenotype or genotype of N-acetyltransferase 2, which is largely responsible for isoniazid metabolism. In conclusion, we found the prevalence of anti-TB drug-induced hepatitis in our population in Malaysia to be 9.7%. The presence of HIV infection, lower pretreatment serum albumin, higher pretreatment serum globulin and EPTB were significant at univariate analysis, but only underlying HIV infection and EPTB were independent risk factors for the development of drug-induced hepatitis by multivariate logistic regression analysis.

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