The Prevalence and Factors Associated with Drug-induced Hepatitis in HIV-positive Tuberculosis Patients

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ABSTRACT

Introduction: *Tuberculosis (TB) have demonstrated a global increase since 1990 along with the increase of world's population and the transmission of human immunodeficiency virus (HIV). Anti-tuberculosis drugs are very effective, but it may cause drug-induced hepatitis (DIH). The aim of this study was to assess the prevalence and association of several risk factos with the occurence of drug-induced hepatitis in HIV-positive tuberculosis patients.*

Method: *We conducted a retrospective case-control study based on medical records of HIV-positive TB patients who seek medical attention to HIV Referral Center at Cipto Mangunkusumo Hospital between July 2008 and December 2010. Overall, we enrolled 168 medical records with 42 cases and 126 controls. Chi-square and logistic regression test analysis were conducted for analyzing risk factors of drug-induced hepatitis in HIV-positive tuberculosis patients.*

Results: *Drug-induced hepatitis were found in 42 (8.04%) patients.The prevalence of DIH was highest among 35 (25.2%) male patients, aged < 35 years old in 32 (26.0%) patients, with albumin level < 3.5 g% in 10 (11.2%) patients, body mass index (BMI) < 18.5 kg/m^2 in 14 (18.4%) patients, CD4+ count < 100 cells/mm^3 in 29 (24.4%) patients, and those who received rifampicin (R), isoniazid (H), and pirazinamid (Z) regiments for their anti-tuberculosis drugs 24 (31.2%) patients. No risk factors were found to have statistically significant association with DIH.*

Conclusion: *The prevalence of DIH is quite high. Although no risk factor was found statistically significant, but evaluation and liver biochemical examination should be carried out regularly in patients with DIH risk factors.*

Keywords*: drug-induced hepatitis, tuberculosis, human immunodeficiency virus*

ABSTRAK

Pendahuluan*: Tuberkulosis (TB) meningkat secara global sejak tahun 1990-an, seiring dengan peningkatan populasi di dunia dan penularan 'human immunodeficiency virus' (HIV). Pengobatan dengan obat anti-tuberkulosis sangat efektif, namun dapat menyebabkan gangguan pada hati atau hepatitis imbas obat. Tujuan penelitian ini adalah untuk menilai prevalensi dan hubungan beberapa faktor risiko dengan kejadian hepatitis imbas obat pada pasien TB-HIV.*

Metode: *Dilakukan studi kasus kontrol dengan menelusuri data rekam medik pasien TB yang mengidap HIV-positif yang datang ke Kelompok Studi Khusus (POKDISUS) Rumah Sakit Cipto Mangunkusumo sejak Juli 2008 sampai Desember 2010. Digunakan uji kai kuadrat dan regresi logistik pada 168 data rekam medik sebagai sampel yang terdiri dari 42 kasus dan 126 kontrol untuk menilai faktor risiko terjadinya hepatitis imbas obat pada pasien TB-HIV.*

Hasil: *Hepatitis imbas obat ditemukan pada 42 (8,04%) pasien. Prevalensi hepatitis imbas obat tertinggi ditemukan pada 5 pasien pria (25,2%), pasien usia < 35 tahun sejumlah 32 (26,0%) orang, pasien dengan kadar albumin < 3,5 g% sejumlah 6 (11,2%) orang, pasien dengan indeks masa tubuh < 18,5 kg/m^2 sejumlah 14 (18,4%),*

pasien dengan kadar CD4+ < 100 cells/mm³ sejumlah 29 (24,4%) orang, dan pada mereka yang mendapatkan regimen obat anti-tuberkulosis (OAT) rifampisin, isoniazid, dan pirazinamid sejumlah 25 (31,2%) pasien. Tidak satupun dari faktor risiko tersebut terbukti memiliki hubungan bermakna dengan kejadian hepatitis imbas obat.

Simpulan: *Prevalensi hepatitis imbas obat masih cukup tinggi. Meskipun tidak satupun faktor dalam penelitian ini terbukti bermakna berhubungan dengan kejadian hepatitis imbas obat, namun evaluasi dan pemeriksaan biokimiawi fungsi hati tetap harus rutin dilakukan pada pasien yang memiliki faktor risiko untuk mengalami hepatitis imbas obat.*

Kata kunci: *hepatitis imbas obat, tuberkulosis, human immunodeficiency virus*

INTRODUCTION

Tuberculosis (TB) affects one third of the world's population.[1] As an immune-related disease, *Mycobacterium tuberculosis* (MTB) infection is facilitated by immunocompromised status. It causes individuals with immune deficiency to develop a greater risk of TB. One of the high-risk group is individual with human immunodeficiency virus-infection.[2]

The World Health Organization (WHO) estimates that TB is the cause of death for 11% of all acquired immunodeficiency syndrome (AIDS) patients. In 2006, it was estimated that over 700,000 people had suffered from HIV-associated TB; of whom, about 200,000 have died.[3] Anti-tuberculosis treatment with isoniazid, rifampicin and pyrazinamide are very effective.[1] In the United States, the percentage and absolute number of patients with TB disease who are HIV-1 infected is declining because of improved infection-control with anti-tuberculosis treatment equiped by voluntary counseling and testing.[2] Therefore, many efforts regarding this issue have been conducted, which include screening for TB in people living with HIV, isoniazid preventive therapy (IPT), and infection control.[3] Nevertheless, treatment with anti-tuberculosis drugs may also cause hepatotoxicity.

It has been known that individuals with immune deficiency are more likely develop drug-induced hepatitis (DIH) compared to those of normal population. Marzuki et al, has shown that HIV positivity was a significant factor for developing anti-tuberculosis DIH.[1] Dealing with this problem, Center for Disease Control and Prevention (CDC), the National Institutes of Health, and the HIV Medicine Association (HIVMA) and Infectious Diseases Society of America (IDSA) recommend to conduct gradual liver function test for HIV patients receiving treatment of anti-tuberculosis.[2] Sufficient information about the prevalence and associated factors of drug-induced hepatitis in TB-HIV patients is also required for establishing early diagnosis and providing prompt treatment. Therefore, this study aim was to obtain the prevalence and several factors associated with DIH in HIV-positive tuberculosis patients in Cipto Mangunkusumo Hospital.

METHOD

Between July 2008 and December 2010, a retrospective case-control study was conducted at HIV Referral Centre of Cipto Mangunkusumo Hospital that served as referral and treatment centers for HIV and TB in Indonesia. This study attempted to explore whether several demographic, clinical, laboratoric characteristics had a correlation with DIH among patients with co-infection HIV and tuberculosis who received anti-tuberculosis regiments.

Medical records of 372 HIV-positive TB patients at the outpatient clinic who were having anti-tuberculosis therapy were evaluated. Tuberculosis was diagnosed based on clinical criteria (chronic cough which last more than two weeks, prolonged fever, extreme weight loss, and night sweating), as well as radiological and laboratoric (alcohol acid fast bacilli) evidence; while hepatotoxicity was diagnosed on the present of nausea, vomitus, weakness, and jaundice along with high concentration of AST/ALT. Additional inclusion criteria included patients whose medical file showed normal results of AST/ALT test before the treatment of anti-tuberculosis regiments. Medical records with uncomplete data or elevated AST/ALT level before starting tuberculosis treatment were excluded from the study.

This was a retrospective case-control study since there was a time interval between the prescription of anti-tuberculosis regiment and the occurence of DIH. We took the equal population, i.e. HIV-infected individuals as the control group in order to minimize bias (ratio 1 : 3).

A total of 372 medical records of patients co-infected with HIV and tuberculosis receiving anti-

tuberculosis regiment were collected. Among them, 42 subjects developed DIH; while the other 330 subjects did not present those effects. Of those who did not develop DIH, 126 subjects were randomly selected as the control group. Data was cleaned for inconsistencies and missing values, which subsequently was analyzed using SPSS 16.0 statistical software. Chi-square test was used to evaluate the association between the abovementioned characteristics and the prevalence of DIH in HIV-positive TB patients who received anti-tuberculosis regiment. All variables with significant association in bivariate analysis ($p < 0.25$) were candidates to be included in the final multivariate analysis by using logistic regression test.

RESULTS

Three hundred and sixty two patients were enrolled in the study. Among them, 42 subjects developed DIH (8.04%). Based on demographic characteristics, the prevalence of DIH was highest among male subjects (25.2%) and aged < 35 years old (26.0%).

Considering the baseline clinical characteristics, this study showed that DIH were more frequent

Table 1. Bivariate analysis on demographic and clinical characteristics associated with DIH in HIV-positive tuberculosis patients

Variable	DIH (n = 42) n (%)	Non DIH (n = 126) n (%)	OR (95% CI)	p*
Age (year)				
< 35	32 (26.0)	91 (74.0)	0.812	0.615
≥ 35	10 (22.2)	35 (77.8)	(0.361-1.826)	
Sex				
Male	35 (25.2)	104 (74.8)	0.945	0.906
Female	7 (24.1)	22 (75.9)	(0.372-2.403)	
Extrapulmonary tuberculosis				
Yes	1 (11.1)	8 (88.9)	0.360	0.453
No	41 (25.8)	118 (74.2)	(0.044-2.964)	
Pulmonary tuberculosis				
Yes	27 (24.8)	82 (75.2)	0.966	0.926
No	15 (25.4)	44 (74.6)	(0.466-2.004)	
Pulmonary and extrapulmonary tuberculosis				
Yes	12 (31.6)	26 (68.4)	1.538	0.287
No	30 (23.1)	100 (76.9)	(0.694-3.412)	
Milliary tuberculosis				
Yes	2 (16.7)	10 (83.3)	0.580	0.489
No	40 (25.6)	116 (74.4)	(0.122-2.760)	
BMI (kg/m$^{2)}$				
< 18.5	14 (18.4)	62 (81.6)	0.660	0.340
≥ 18.5	13 (25.5)	38 (74.5)	(0.280-1.554)	
Anti-tuberculosis regiment				
RHZE				
Yes	22 (29.3)	53 (70.7)	1.836	0.244
No	20 (21.5)	73 (78.5)	(0.906-3.721)	
RHZ				
Yes	24 (31.2)	53 (68.8)	1.836	0.089
No	18 (19.8)	73 (80.2)	(0.906-3.721)	

BMI: body mass index; RHZE: rifampicin, isoniazid (INH), pyrazinamide, etambutol; DIH: drug-induced hepatitis; *chi-square test

Table 2. Bivariate analysis on laboratory findings associated with DIH in HIV-positive tuberculosis patients

Variable	DIH (n = 42) n (%)	Non DIH (n = 126) n (%)	OR (CI 95%)	p*
Hepatitis B (HBsAg)				
Yes	6 (37.5)	10 (62.5)	1.917	0.183
No	36 (23.8)	115 (76.2)	(0.651-5.639)	
Hepatitis C (anti-HCV)				
Yes	18 (20.7)	69 (79.3)	0.609	0.166
No	24 (18.0)	56 (70.0)	(0.301-1.233)	
HBsAg and anti-HCV				
Yes	0 (0.0)	5 (100.0)	-	0.333
No	42 (25.8)	121 (74.2)		
Albumin (g/dL)				
< 3.5	10 (11.2)	79 (88.8)	0.970	0.956
≥ 3.5	6 (11.5)	46 (88.5)	(0.331-2.845)	
CD4+ (cell/mm^3)				
< 100	29 (24.4)	90 (75.6)	2.014	0.220
100-200	4 (13.8)	25 (86.2)	(0.647-6.268)	
AAFB				
Positive	3 (20.0)	12 (80.0)	0.964	0.959
Negative	14 (20.6)	54 (79.4)	(0.239-3.891)	

DIH: drug-induced hepatitis; HBsAg: hepatitis B surface antigen; anti-HCV: anti-body hepatitis C virus; AAFB: alcohol acid fast bacilli; *chi-square test

Table 3. Multivariate analysis on factors associated with DIH in HIV-positive tuberculosis patients

Variable	OR (95% CI)	p*
Hepatitis C	0.036-1.517	0.381
Hepatitis B	0.601-5.442	0.292
CD4+	0.332-1.885	0.597
RHZE	0.906-3.721	0.999
RHZ	0.906-3.721	0.999

RHZE: rifampicin, INH, pyrazinamide, etambutol; DIH: drug-induced hepatitis; *logistic regression test

among those of pulmonary tuberculosis group and low body mass index (BMI) < 18.5 kg/m^2. Most of them had albumin level of < 3.5 g% (11.2%), CD4+ counts of < 100 cells/mm^3 (24.4%), and received RHZ regiments for their anti-tuberculosis treatment (31.2%), as seen in Table 1. Statistical analysis (bivariate and multivariate) did not found any risk factors to be statistically significant as risk factor for DIH, as seen in Table 2 and 3.

DISCUSSION

In the present study, we explored demographic, clinical, and laboratoric characteristics to assess whether those factors are associated with DIH in HIV-positive TB patients who were seeking medical treatment at HIV referral center Cipto Mangunkusumo Hospital.

There are several previous reports which focused on assessing factors associated with DIH; however, those reports have not demonstrated results on specific population such as HIV-related TB patients, HIV-positive TB patients were only placed into subgroup to be compared with another group.[1,4-8] Results revealed from those studies stated that HIV positivity in patients receiving anti-tuberculosis agent was significant for higher risk of developing DIH.

Based on demographic profile, subjects of this study were mostly male patients among both group (25.2% of case group and 74.8% of control group). It is consistent with a study in Brazil, which even demonstrated higher percentage (56.1% of case group and 77.6% of control group). This study results were in contrast to another study comparing the incidence of hepatotoxicity between group of patients receiving anti-tuberculosis and antiretroviral drugs, which their multivariate analysis showed significant correlation between sex characteristic and the incidence of hepatotoxicity with a greater risk in female patients (p = 0.219; OR = 4.2).[9]

We also found that patients aged < 35 years old (26.0%) were most likely to develop DIH. The findings are consistent with a study in Ethiopia comparing the incidence based on HIV status.[10] Similar study in Thailand also found that their subject mostly belong to the mean age of 35 years old.[9] However, these findings were contrast to several studies showing that age was found to be a risk factor for DIH. Another study has reported that hepatotoxicity ranges from 22 to 33% in those subjects who were older than 35 years, compared with 8 to 17% in those who were younger than 35 years.[11]

It has been known that there is an association between a low BMI with the development of TB in HIV patients. First, TB could lead to malnutrition through

anorexia. Increased metabolic rate, malabsorption and any immune impairment as a result of HIV/AIDS leads to malnutrition.[12,13]

On the other hand, malnutrition in HIV patients can aggravate immune deficiency and subsequently increase the risk of active TB. As we have known, malnutrition can cause liver damage through a chronic process. Theoretically, it explains why drug-induced hepatotoxicity occurs more easily in co-infected patients with lower BMI. In this study, the results based on baseline clinical characteristics showed that DIH were more frequent among those of pulmonary tuberculosis group and low BMI (< 18.5 kg/m^2). However, in this study, there was no significant difference in BMI among subjects in the case group, i.e. there were 14 patients who had BMI lower than 18.5 kg/m^2 and 13 patients with BMI more than 18.5 kg/m^2. A larger percentage of low BMI in patients presented with hepatotoxicity was found in a study among Ethiopian patients, i.e. 58.7% of 184 patients. Similar results were also found for other studies in Ethiopia and Thailand.[9,10]

It might occur since the high incidence of TB in HIV patients was mostly found in subjects with low BMI and pulmonary TB is the most common type of TB found in HIV patients. This study showed similar findings to one study in Ethiopia based on CD4+ counts, which demonstrated that the distribution of anti-tuberculosis DIH were mostly found among them with CD4+ counts < 100 cells/mm^3 (24.4%).[10] It could be explained since CD4+ counts < 100 cells/mm^3 represents worse immune deficiency. Based on the anti-TB regiment, this study showed that the high incidence of TB in HIV patients was mostly found among subjects receiving rifampicin, isoniazid (INH), and pyrazinamide (31.2%); while other studies found that the incidence mostly belongs to the group receiving anti-tuberculosis regiments of streptomycin, rifampicin, INH, and pyrazinamide (SRHZ).[10]

HIV-infected individuals are not only at risk for tuberculosis but also at risk for hepatitis B and or C infection. These infections attack the liver and may influence susceptibility of the organ to injury caused by hepatotoxic drugs such as anti-tuberculosis and antiretroviral drugs.

HIV positivity has been found to be a risk factor for DIH and the occurrence of hepatitis C co-infection has augmented the condition. In contrast, another study showed that hepatitis B infection were not found to be statistically significant with DIH.[4] It is consistent with these findings that 18 of 42 co-infected patients with DIH had hepatitis C infection, while only 6 of them had hepatitis B infection. Another study found that HIV-positive TB patients who received anti-tuberculosis regiment and developed DIH showed a significantly higher frequency of co-infection with hepatitis B or C on bivariate and multivariate analysis ($p < 0.001$) with an odds ratio of 21.73 (95% CI = 2.71-174.18).[14]

Multivariate and bivariate analysis in this study showed that no factor was statistically significant regarding its association with DIH in HIV-positive TB patients. Retrospective data collection is a limitation of this study. It enables the occurence of bias since those medical records were filled in by different physicians. Moreover, there were some medical records with incomplete data. However, the prevalence of DIH in some patients calls for greater concern since tuberculosis is a major problem in HIV; while on the other hand, anti-retroviral and anti-tuberculosis drugs has a sinergic hepatotoxicity effect. Therefore, in the near future, it is highly appreciated for gastroentero-hepatologist to be involved in the integrated management of HIV patients. Further cohort study is recommended to obtain more reliable information about risk factors associated with the incidence of DIH and early detection for hepatic injury in HIV-positive TB patients who are on anti-tuberculosis treatment. This allows physician to be aware when prescribing anti-tuberculosis regiments to HIV-positive TB patients who have risk factors for DIH.

CONCLUSION

The prevalence of DIH is quite high, which was found mostly in male patients, and those with low albumin, BMI, and CD4+ count. Despite no significant risk factors were found to be associated with the incidence of DIH in HIV patients, evaluation and liver bio-chemical examination still should be carried out regularly in HIV patients receiving anti-tuberculosis regiments.

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