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CONTENT

Adverse Events During Treatment of Multidrug-Resistant Tuberculosis: The First Cohort Event Monitoring in Vietnam

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Abstract

Introduction: The safety data during multidrug-resistant tuberculosis (MDR-TB) treatment have varied for not only Vietnamese patients but also patients in other areas of the world. ***Objectives:*** This study was conducted to determine the incidence of adverse events (AEs) that occurred during MDR-TB treatment in Vietnam and to assess risk factors associated with adverse events. ***Methods:*** AEs were collected from 659 MDR-TB patients enrolled from April to December 2014 through a cohort event monitoring (CEM) program. Patients were monitored with a follow-up of approximately 20 months. Adverse events were determined by clinical criteria and laboratory tests. Cox proportional hazard regression models were used to explore factors associated with the reported adverse events. ***Results:*** The cohort enrolled 659 patients in which 81.3% experienced at least one AE during treatment. Of those with AEs, 18.3% required adjustment of MDR-TB regimen. The most common AEs including arthralgia, hepatotoxicity and hyperuricemia were observed in 34.7%, 32.2% and 29.3% of patients, respectively. Multivariate regression analysis indicated that the independent predictors for hepatotoxicity were baseline levels of alanin amino transferase (HR 1.023; 95%CI 1.008-1.037) and alcoholic status (HR 4.255; 95%CI 1.239-14.616) while pyrazinamide daily dose (HR 1.025; 95%CI 1.002-1.048) and alcoholic status (HR 2.016; 95%CI 1.084-3.751) were associated with the elevation of serum uric acid. ***Conclusions:*** Adverse events were common during MDR-TB treatment in Vietnam including serious ones that required proper interventions. Predictors for hepatotoxicity and hyperuricemia observed in this study underlined the importance of patient history investigation, baseline physical and laboratory examination and close monitoring.

Keywords: MDR-TB; cohort event monitoring; adverse event; Vietnam

1. INTRODUCTION

The complicated epidemiological situation of drug-resistant TB in Vietnam as well as in other countries has been a global concern and become a great challenge for our efforts to control TB [1]. TB treatment requires long term chemotherapy with a combination of many antibiotics simultaneously, so problems related to drug safety, especially severe adverse events, can cause a great impact on treatment adherence, thus leading to drug resistance and difficulty in monitoring TB. As a result, ensuring safe and rational drug use has been considered as one of the most important objectives of MDR-TB treatment. Activities that monitor, detect, evaluate and prevent adverse drug reactions related to drugs against TB hold important roles in the enforcement of treatment efficiency, saving costs, preventing drug resistance and contributing in patients life quality [2]. To date, the rates of yearly spontaneous reports received by the National DI & ADR Center related to MDR-TB drugs are rather low and does not reflect the safety of MDR-TB treatment in Vietnam [3]. Thus, it is not possible to detect problems related to drug safety and to provide data for recommendations on regimen change. Consequently, the implementation of programs enforcing the collection of ADR reports the evaluation of ADR from MDR-TB drugs is becoming more urgent.

This study may help determine the incidence of adverse events (AEs) that occurred during MDR-TB treatment in Vietnam. We also aim to assess risk factors associated with the occurrence of the most reported adverse events.

2. METHODS

2.1 Study design

We conducted an observational, prospective study based on a Cohort Event Monitoring (CEM) program.

2.2 Setting and study population

Nine TB treatment centers in Vietnam were chosen as sentinel sites of the study. The targeted population of this study was adult (≥ 16 year-old) patients starting MDR-TB treatment at chosen sentinel sites and enrolled between April 2014 to December 2014. Patients taking part in other studies (e.g. the STREAM trial) were excluded.

2.3 Treatment protocol and follow-up

Patients treated in sentinel sites received MDR-TB therapy based on drug susceptibility test (DST) results and their treatment history. The standardized regimens (IVa and IVb) consisted of six drugs: kanamycin (or capreomycin), levofloxacin, prothionamide, cycloserine (or p-aminosalicylic acid PAS), pyrazinamide and ethambutol. The only difference between IVa and IVb regimens was the injectable drugs. A standardized regimen would be modified based on DST results and history of allergy.

Patients were treated for MDR-TB for up to 24 months. At each clinic visit, the patient was examined for treatment response and undesirable effects. Patients were assessed by clinical and sub-clinical manifestations at baseline (before starting MDR-TB treatment), during routine follow-up visits (once a month) and at any time that AEs occurred/were reported. Table 1 shows the definitions of important adverse drug reactions from scientific medical literature regarding all of MDR-TB drugs in the standardized regimens.

2.4 Data collection and analysis

Information was filled into paper collection forms, afterwards transfered to Microsoft® Access 2010 then to SPSS® Statistics 22. For descriptive statistics, nominal and ordinal variables were presented as percentages, continuous variables with normal distribution were represented as mean ± SD (standard deviation). Cox multivariate regression analysis was conducted using stepwise backward method to look for independent factors associated with AEs due to MDR-TB therapy.

2.5 Ethics

As this was a study of routinely collected monitoring data and did not affect therapeutic practice, informed consent from the patients was not obtained.

Table 1. *Definitions of adverse events of MDR-TB standardized regimens*[4]

Adverse event	Definition
Hepatoxicity	
Identified	Presence of jaundice, conjunctival discolouration, nausea, vomiting, loss of appetite, urine abnormal, abdominal pain, pruritus and elevated AST or ALT level > 3 ULN*, or AST or ALT level > 5 ULN without symptoms or diagnosed with hepatotoxicity by physician.
Suspected	Presence of one or some symptoms but no findings to confirm the diagnosis.
Psychiatric disorders	Presence of one or more of the followings: paranoid reaction, delusion, abnormal behaviour, bad mood lasts over 2 weeks, insomnia, distraction, suicide attempt or other psychiatric symptoms, unless the cause was known such as TB in the central nervous system, cerebrovascular accident, alcoholism.
Arthralgia	Presence of joint pain, unless the cause was known, e.g. musculoskeletal tuberculosis, rheumatoid arthritis…
Hypersensitivity reactions	Presence of one of the followings: pruritus, rash, photosensitivity or other hypersensitivity reactions including anaphylaxis, unless the cause was known, e.g. food allergy, hepatitis…
Renal toxicity	Presence of oliguria, oedema, at least one elevated serum level of creatinine, urea after starting MDR-TB treatment, creatinine clearance < 50 ml/min or diagnosed by physician.
Vision disorders	Vision abnormal or decrease eyesight after starting MDR-TB treatment or difficult to distinguish colour with no other symptoms or diagnosed by physician.
Hearing and vestibular disorders	Deaf or hearing loss after starting MDR-TB treatment or diagnosed by physician or confirmed by audiometry; symptoms consistent with vestibular disorders such as vertigo and/or loss of balance.
Hypothyroidism	
Identified	Presence of fatigue, tiredness, depression, constipation, arthralgia, excessive menstrual bleeding, distraction, loss of appetite, weight gain, dry skin, dry hair, and elevated TSH level > 5 uU/l, T3 level < 1 nmol/l, T4 level < 64 nmol/l.
Suspected	

	Presence of one or some symptoms but no findings to confirm the diagnosis
Hypokalemia	At least one serum potassium value ≤ 3,5 mmol/l.
Hyperuricemia	Serum uric acid level > 420 umol/l (70 mg/dl) in men and > 360 umol/l (60 mg/dl) in women or diagnosed by physician.
Blood disorders	Anemia (hemoglobin < 12 g/dL in men and < 13 g/dL in women) or leucopenia (< 3000 x 10^9/l) or thrombocytopenia (< 100 x 10^9/l) or diagnosed with blood disorders by physician.

**ULN: Upper Limit of Normal*

3. RESULTS

3.1 Patient characteristics

Properties and characteristics of the cohort are presented in Table 2. Between April 2014 and December 2014, 659 patients were enrolled in the study. Of these, 631 (95.8%) patients were treated with regimen IVa, 22 (3.3%) and 6 (0.9%) patients received regimen IVb and individualized therapy, respectively. The median duration of MDR-TB therapy was 19.2 months (Interquartile range [IQR] 17.5 - 20.2).

Table 2. *Characteristics of patients treated with MDR-TB therapy (n = 659)*

Characteristics	**n (%)**
Male sex	517 (78.5)
Age (year). mean ± SD	42.4 ± 13.8
Weight (kg). mean ± SD	48.3 ± 9.3
Baseline conditions	
Diabetes mellitus	104 (15.8)
HIV co-infection	57 (8.7)
Hepatic disease	33 (5.0)
Renal insufficiency	5 (0.8)
Alcoholism	16 (2.4)
History of allergy	13 (2.0)
Number of months on treatment. median [IQR]	19.2 (17.5 - 20.2)
Treatment outcome	
Cure/completion	512 (77.7)
Transfer-out	17 (2.6)
Default	61 (9.3)
Failure	20 (3.0)
Death	49 (7.4)

3.2 Adverse events

Overall, at least one type of AE was experienced by 536 (81.3%) of 659 MDR-TB patients. Table 3 demonstrates the frequency and duration of occurence of each type of adverse event in this cohort. The most common types of AE were arthralgia (34.7%) and hepatotoxicity (32.2%), respectively. Out of those patients experienced AEs, 18.3% of patients required a significant change in MDR-TB chemotherapy due to adverse events: dose reduction (5.2%), temporary discontinuation (10.1%), and drug substitution (3.0%).

Table 3. *Frequency of significant adverse events observed during MDR-TB treatment*

Type of AE	Patients experienced AE (n = 659) n (%)	Type of AE	Patients experienced AE (n = 659) n (%)
Arthralgia	229 (34.7)	Vision disorders	69 (10.5)
Hepatotoxicity	212 (32.2)	Hypokalemia	60 (9.1)
Nausea, vomiting	210 (31.9)	Peripheral neuropathy	52 (7.9)
Hyperuricemia	193 (29.3)	Abdominal pain	47 (7.1)
Anorexia	188 (28.5)	Hyperglycaemia	42 (6.4)
Dizziness	151 (22.9)	Hematologic disorders	23 (3.5)
Headache	127 (19.3)	Diarrhea	20 (3.0)
Dermatologic disorders	119 (18.1)	Hypothyroidism	15 (2.3)
Gastritis	116 (17.6)	Convulsions	10 (1.5)
Octotoxicity	100 (15.2)	Anaphylaxis	4 (0.6)
Psychiatric disorders	94 (14.3)	Vision disorders	69 (10.5)
Nephrotoxicity	85 (12.9)	Hypokalemia	60 (9.1)

3.3 Risk factors

Multivariate regression model was used to assess risk factors on the most reported adverse events including hepatotoxicity, arthralgia and hyperuricemia (Table 4). While male gender ($p = 0.019$), alcoholic status ($p = 0.011$) and baseline AST ($p = <0.001$) were found to be associated with suspected hepatotoxicity, independent factors associated with the development of identified hepatotoxicity were baseline ALT ($p = 0.002$) and alcoholism ($p = 0.021$). Pyrazinamide daily dose ($p = 0.034$) and alcoholic status ($p = 0.027$) were associated with the elevation of serum uric acid. No factors in relation with the occurrence of arthralgia were found to be statistically significant.

Table 4. *Multivariable analysis of factors associated with adverse events*

Adverse events	Variable	Cases[1] n (%)	Controls[2] n (%)	p value	HR	(95% CI)
Suspected hepatotoxicity	*Sex*					
	Male	155 (85.6)	362 (75.7)	**0.019**	1	
	Female	26 (14.4)	116 (24.3)		0.593	(0.384-0.916)
	Alcoholism					
	No	173 (95.6)	470 (98.3)	**0.011**	1	
	Yes	8 (4.4)	8 (1.7)		2.512	(1.231-5.129)
	Baseline AST (U/L)			**<0.001**	1.005	(1.002-1.007)
Identified hepatotoxicity	*Age (year)*			0.074	1.026	(0.998 -1.056)
	Alcoholism					
	No	28 (90.3)	615 (97.9)	**0.021**	1	
	Yes	3 (9.7)	13 (2.1)		4.255	(1.239-14.616)
	Baseline AST (U/L)			0.083	0.983	(0.963-1.002)
	Baseline ALT (U/L)			**0.002**	1.023	(1.008-1.037)
Hyperuricemia	*Alcoholism*					
	No	180 (93.3)	463 (99.4)	**0.027**	1	
	Yes	13 (6.7)	3 (0.6)		2.016	(1.084-3.751)
	Diabetes mellitus					
	No	178 (92.2)	377 (80.9)	0.057	1	
	Yes	15 (7.8)	89 (19.1)		0.563	(0.311-1.017)
	Pyrazinamid daily dose (mg/kg per day)			**0.034**	1.025	(1.002-1.048)

[1]experienced AE; [2]not experienced AE; HR: hazard ratio.

5. DISCUSSION

This study was not only the first cohort event monitoring but also the largest study to date of MDR-TB treatment in Vietnam. It was based on an active surveillance system with designed forms, had a large sample size, and provided valuable information about adverse events in Vietnamese population.

Initially, we found that 81.3% of patients developed at least 1 type of AEs after MDR-TB treatment. The frequency of adverse events in our study was rather higher than that in previous studies. A study in Russia of 244 MDR-TB patients showed that 73.3% patients had experienced at least one adverse event [5]. The rate of patients experienced AEs in an observational cohort study on drug resistant TB in Pakistan was 72.3% [6]. A cross-sectional study on the treatment of MDR-TB patients in Vietnam observed 143 (50.7%) patients with at least one adverse event [7]. There were several factors that may have contributed to this result. Firstly, unlike restropective studies with high probability of missing data, this study method allowed us to collect and record information more properly. Secondly, patients enrolled in the study were monitored regularly during treatment by trained healthcare workers following a complete procedure, thus increasing the ability of detecting adverse events. In addition, a list of definitions was compiled with detailed descriptions of expected adverse reactions of MDR-TB medication to optimize AE detection. Therefore, the results of this study could reflect the incidence of adverse reactions following standardized MDR-TB therapy in Vietnam.

The severity of AEs varied from mild rash or nausea to the life-threatening anaphylaxis. The most common adverse events were arthralgia (34.7%), hepatotoxicity (32.2%), nausea/vomiting (31.9%), hyperuricemia (29.3%) and anorexia (28.5%). Arthralgia and gastrointestinal disorders were consistent with other published studies as the most reported. In Nathanson et al., the most observed adverse events were nausea/vomiting (32.8%), diarrhea (21.1%) and arthralgia (16.4%)[8]. In Hoa et al., the most common undesirable reactions of MDR-TB drugs were arthralgia (35.8%), followed by gastrointestinal disturbance (14.2%) [7]. Other clinically significant adverse events were also observed such as ototoxicity (15.2%), psychiatric disorders (14.3%), nephrotoxicity (12.9%), vision disorders (10.5%) and hypokalemia (9.1%).

Both of arthralgia and hyperuricemia were common in our study and probably related to each other. Hyperuricemia, in fact, may potentially lead to severe gouty arthritis if it is not under control, and therefore, should not be underestimated. Although many studies have showed arthralgia as one of the most reported undesirable effects during MDR-TB treatment, hyperuricemia seems to be not significant enough to be noticed.

In a systematic review on adverse events of MDR-TB drugs, we found that out of 69 studies, there were 35 studies had observed arthralgia/joint pain but hyperuricemia was presented in only 2 studies [9]. Besides, the rates of hyperuricemia in those studies were quite low: 2.8% [10] and 12.6% [11]. The results of multivariable analysis also indicated that alcoholism and pyrazinamide daily dose could affect on serum uric acid level, suggesting that this drug should be prescribed according to body weight.

In this study, hepatic adverse events were reported in 212 (32.2%) of patients. However, only 31 (4.7%) patients were classified as identified hepatotoxicity. A study on hepatic events during MDR-TB treatment in Russia, in which 91/658 (16.5%) patients experienced hepatoxicity, showed that elevated transaminases (ALT, AST) at baseline were associated factors of hepatotoxicity [12]. The results of our study confirmed that baseline levels of ALT was one of the independent predictors for identified hepatotoxicity, which can be explained because an increase in ALT serum levels, compared to AST, is more specific for liver damage [13].

One of the limitations of our study was the lack of consistency in detecting and reporting AEs among nine sentinel sites, which was caused by their differences in human and technical resources. Moreover, some types of AE requiring specific measurements (e.g. audiometry) might be underestimated. In spite of these limitations, the results are encouraging and we believe that our study has provided important information regarding the side effects of second-line anti-TB drugs in Vietnam. The methodology of this study could be applied to other studies especially for new drugs, or standardized yet high-cost regimens.

5. CONCLUSIONS

Adverse events were encountered in most patients during MDR-TB treatment in Vietnam and may result in treatment change. The findings in this study demonstrate that adverse events can be detected in a timely and effective way through baseline examination and routine monitoring. On the basis to understand the significance of undesirable effects in MDR-TB treatment, further investigation is suggested to emphasizing the occurrence of adverse events in different phases of MDR-TB treatment, and corresponding relationships with other risk factors.

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