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Recurrent drug-induced hepatitis in tuberculosis-comparison of two drug regimen

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Abstract

Drug-induced hepatitis (DIH) is one of the major complications amongst the treatment of patients with tuberculosis (TB); it might even be fatal. This study tries to address the recurrence of DIH with two anti-TB regimens.

In the retrospective study from 2007 to 2010, 135 TB patients with DIH who were older than 16 years old were entered to study. The patients with DIH were randomly treated with a regimen including isoniazid, rifampin and ethambutol, plus one of ofloxacin or pyrazinamide. The patients were reviewed for occurrence of recurrent drug-induced hepatitis. Cure and completed treatment was considered as an acceptable treatment outcome while default of treatment, treatment failure and death were considered to be as unacceptable outcome. So, 135 subjects with DIH were reviewed, 23 (17%) patients experienced recurrence of hepatitis (19 cases in the ofloxacin group and 4 cases in the Pyrazinamide group). There is no significant difference in recurrence of hepatitis between these two groups ($P = 0.803$). An acceptable outcome was observed in 95 patients (70.4%) and an unacceptable outcome was seen in 14 cases (10.3%). There was no significant difference in outcomes between these two regimens. ($P = 0.400$, $OR = 1.62$, CI 95% 0.524-4.98).

The results of our study suggest that ofloxacin-based anti-TB regimen does not decrease the risk of recurrent drug-induced hepatitis. Therefore, adding ofloxacin in the case of DIH is not recommended.

Keywords

Drug-induced hepatitis; Mycobacterium Tuberculosis; Ofloxacin; Pyrazinamide

2. Introduction

Human tuberculosis (TB) has caused 1.5 million deaths around the world only in 2013. This alarming mortality rate ranks TB as a leading cause of death from treatable infectious diseases.[1] Despite of over fifty years history of anti-TB chemotherapy, the corner stone of anti-TB treatment is six-month therapy with isoniazid(INH), rifampin(RIF), pyrazinamide(PZA) and ethambutol(ETB).[2] Adherence to treatment has a pivotal role in the management of TB, where the complications of treatment make it difficult.[3] Among these, drug induced hepatitis (DIH) is one of the major obstacles of TB treatment which can even be fatal.[4] Reduction of adherence to treatment is an important challenge in TB control programs in both developed and developing countries.[5, 6] In this case, drug hepatotoxicity can cause default of treatment, and/or prolonged hospital stay.

Standard TB treatment is based on at least three hepatotoxic drugs including isoniazid, rifampin and pyrazinamide. These factors include things such as excessive use of alcohol, older age, female sex, malnutrition, human immunodeficiency virus (HIV), viral hepatitis and liver diseases increase the risk of DIH. In our practice, majority of patients have at least one of these risk factors.[7-11] In this regard, monitoring with liver function tests is recommended by American Thoracic Society in alcohol consumers, chronic hepatitis B or C, HIV infected patients and those who have elevated baseline transaminase levels with underlying liver disease.[12]

Although fluoroquinolones are not recommended as first-line standard anti-TB drugs, they have been used as salvage treatment of drug-resistant tuberculosis and considered as a substitute regimen for drug intolerance.[13, 14] Previous published researches are limited in comparison between prescription of ofloxacin and other standard anti-TB drugs regarding liver injury during the course of therapy. Therefore, in order to assess the differences in the rate of recurrent drug induced hepatitis between these two regimens. The medical records of TB patients were examined for recurrence of drug-induced liver injury when treated with Ofloxacin replacement regimen.

3. Material and Methods

The retrospective descriptive study was conducted in Masih Daneshvari hospital, a referral centre for tuberculosis and lung diseases in Tehran. Throughout three-year duration, confirmed pulmonary TB patients who developed drug-induced hepatitis were evaluated for recurrence of drug-induced hepatitis. Tuberculosis was confirmed by positive culture for mycobacterium tuberculosis (Mtb), acid-fast bacilli in sputum smear or DNA polymerase chain reaction with clinical correlation, which is according to WHO guideline.[15]

Liver function tests were performed on all patients on the first day of hospitalization. During their hospitalization, in the case of high liver enzymes level and clinical symptoms of hepatitis, further investigation with liver ultrasound examination, serologic tests for hepatitis B and C virus infection and HIV serology was performed.

Drug induced hepatitis was defined as three-fold increase in ALT enzyme level in addition to clinical symptoms including nausea, vomiting, abdominal pain, jaundice, fatigue and

weakness. Also a five-fold increase in liver enzymes level without clinical signs & symptoms or escalation in total bilirubin up to two-fold was considered as DIH. In the case of liver injury, INH, RIF and PZA were discontinued, while ETB was saved. Then ofloxacin and amikacin were added to the anti-TB regimen, so, the patients were received ETB, ofloxacin and amikacin.[12, 16]

After returning ALT level to normal range (up to 1.5-fold increased level accepted), rifampin was initiated with one-third dose, gradually reached to full dose and amikacin discontinued with rifampin full dose. Then isoniazid and pyrazinamide was prescribed sequentially to reach their maximum daily dose, where in high risk patients, ofloxacin was saved and PZA was not rechallenged. Thus one group of patients received INH, RIF (and ETB) with PZA and another group received INH, RIF (and ETB) and ofloxacin. This selection was based on the patients underlying diseases and condition and, made by the clinicians.

Patients were visited biweekly up to two months after DIH. Cure and completed treatment was considered to be an acceptable treatment outcome while unacceptable outcomes included the default of treatment, treatment failure and death. Types of TB cases (new cases, relapse, inferred in and default of treatment) and TB classification (pulmonary and extra-pulmonary TB) were considered based on WHO definitions.[15]

The patients without complete demographic, clinical, laboratory and treatment outcome were excluded from the study. Statistical analysis was done using SPSS version 16 (SPSS Inc., Chicago, IL, USA). To compare bivariate values, Chi-square and Fisher's exact Test (if applicable) were done. For continuous variables such as age, weight, length of hospitalization, the Kolmogorov-Smirnov test was performed to examine continuousness and then T student test or Chi-square test was done. P-value less than 0.05 ($P < 0.05$) was considered as the significant difference. Methods of study were approved by ethic committee of Masih Daneshvari hospital.

4. Results

4.1 Demographics

A total 135 patients were enrolled with drug induced hepatitis where 67 (49.6%) subjects were male. Patients were between the ages of 16 to 86 years old with mean $\pm$ SD (53 $\pm$ 21). The demographic information is shown in table 1.

4.2 Clinical characteristics

Type of TB cases and TB classification were addressed according to WHO definitions (15) in Table 2. HIV infections were examined in 129 (95.5 %) cases, that 7 (12.6%) cases were positive. The most underlying diseases were diabetes mellitus, hypertension and hepatitis C virus (HCV) infection respectively. In total, 71(52.6%) patients had underlying diseases. (Table 2) There is no significant difference between two groups of drug regimen in terms of TB classification, type of TB, underlying disease conditions, HIV and viral hepatitis status. (Table 2)

4.3 Drug Hepatitis

Twenty three (17%) of total DIH patients (135) were experienced recurrent drug hepatitis, 19 cases with ofloxacin regimen (ofloxacin plus INH, RIF and ETB) and 4 cases with PZA (PZA plus INH, RIF and ETB). Statistical analysis with Chi-square didn't show significant difference between two groups in recurrence of drug induced hepatitis. ($P = 0.803$).

4.4 Treatment Outcome

Treatment outcomes are described in table 2. Comparison of the treatment outcome between ofloxacin and PZA regimens demonstrated that 95 patients (87%) in the ofloxacin group and 21 patients (80%) in the PZA group had an acceptable outcome. There was no significant difference between two groups in acceptable outcome. ($P = 0.400$, OR = 1.62, CI 95% 0.52-4.98). (Table 2)

Total DIH patients (135) and recurrent group didn't show significant difference in terms of sex, age groups, nationality, smoking, opium consumption, underlying diseases and viral hepatitis. (Table 3)

5. Discussion

Tuberculosis is still one of the most threatening infectious diseases in the world and its standard treatment is along with complications such as drug induced hepatitis which can decrease patient adherence to treatment.[15, 17] In undeveloped countries, higher incidence of tuberculosis may cause a higher burden of DIH. Moreover, the incidence of drug induced hepatitis due to anti-TB drugs is higher in these countries.[18] So, this issue is not only important for clinical practitioners to manage the patients illness, but also the burden of this complication should be considered within the health service policy and management.

We did not match the cases and control for study as a clinical trial, but as shown in tables 1 and 2, demographic and clinical characteristics, didn't illustrate significant differences between groups treated with ofloxacin regimen or PZA. Thus, these two groups are proportionate and we can study the effect of drug regimen in recurrent of DIH in this survey. According these results, smoking and use of illegal drugs that is considered risk factors for hepatotoxicity[19], didn't show significant difference between DIH and recurrent DIH group.(Table3)

The results of previous studies about the effect of PZA addition to standard triple-drug regimen (INH, RIF and ETB) on DIH have been incompatible. According to Makhoul et al study, adding PZA didn't change the risk of DIH.[20] This result also has been supported by other studies.[8, 18, 21] But in other studies [5, 15, 22], DIH dramatically rises with adding PZA. So, it seems the effects of one drug in induced liver injury in various contexts, may be very different. Also we should consider that demographic and clinical characteristics should be matched for these studies. For example, it is well known that underlying diseases, particularly viral hepatitis, affect the liver function, [23, 24]. However, in the present study, a significant difference in the underlying disease (comorbidity) between recurrent DIH and DIH group was not seen. (Table 3) Also the study did not report the effect of age and sex in

recurrence of liver injury. Another study by Devarbhavi did not show significant difference by age and sex in anti-tuberculosis drug-induced hepatotoxicity.[25]

The lack of significant difference in recurrent hepatitis between these two groups, suggests that alternative therapy with ofloxacin in all cases is not required. On the other hand, despite less medication side effects and better drug tolerance of ofloxacin, this drug should be saved for patients with some risk factors such as excessive use of alcohol, older age, female sex, malnutrition, HIV infection, underlying liver diseases and viral hepatitis, considering this drug belongs to second line of anti-TB treatment and it is applicable in MDR and XDR TB patients.[26]

This study is limited in patients' selections which were initially chosen in both groups by clinical judgment. But since the significant demographic and clinical characteristics difference was not seen between these two groups, this issue should not affect the conclusion. Also, the number of cases in recurrence of DIH is limited especially in PZA group. Considering that this study is the first comparison of two regimen groups including PZA or ofloxacin, the findings of this study should be validated in a cohort with more patients, in double blind clinical trial.

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Table 1

Demographic profile of patients for the effects of two drug regimens (INH, RIF, and ETB) with ofloxacin or PZA

Variable	Total DIH Patients No(%)	Ofloxacin Group No(%)	PZA Group No(%)	P Value
Sex				
Male	67(49/6)	58(53/2)	9(34/6)	0.08
Female	68(50/4)	51(46/8)	17(65/4)	
Age				
Mean	52.9	53.5	50	0.492
SD±	21.3	21.3	21.4	
Age group				
<35	38(28/1)	30(27/5)	8(30/8)	0.728
35-60	41(30/4)	32(29/4)	9(34/6)	
>60	56(41/5)	47(43/1)	9(34/6)	
Nationality				
Iranian	104(77)	88(80/7)	16(61/5)	0.024
Afghani	30(22/2)	21(19/3)	9(34/6)	
Other	1(0.7)	-	1(3/8)	
Marital Status				
Single	27(20)	22(20/2)	5(19/2)	0.625
Married	76(56/3)	59(54/9)	17(65/4)	
Widow	29(21/5)	25(22/9)	4(15/4)	
Separated	3(2/2)	3(2/8)	-	
Education				
Illiterate	67(49/6)	53(48/6)	14(53/8)	0.848
Literature	32(23/7)	27(24/8)	5(19/2)	
High school diploma	30(22/1)	25(22/9)	5(19/2)	
High Education	6(4/4)	4(3/7)	2(7/7)	
Smoking				
Active smoker	42(31/1)	38(34/9)	4(15/4)	0.032
Passive smoker	8(5/9)	8(7/3)	-	
None	85(63)	63(57/8)	22(84/6)	
Opium Inhalation	34(25/2)	32(29/4)	2(7/7)	0.031
Total	135	109	26	---

Table 2

Patient clinical profile respecting two drug regimens (INH, RIF and ETB) with ofloxacin or PZA

Variable	Total DIH Patients (%)	Ofloxacin Group (%)	PZA Group (%)	P Value
TB classification				
Pulmonary	109(80/7)	88(80/7)	21(80/8)	0.869
Extra-pulmonary	12(8/9)	9(8/3)	3(11/5)	
Pulmonary+ Extra	14(10/4)	12(11)	2(7/7)	
Type of TB cases				
New case	119(88/1)	95(87/2)	24(92/3)	0.457
Relapse	7(5/2)	5(4/6)	2(7/7)	
Inferred in	5(3/7)	5(4/6)	---	
Default of treatment	4(3)	4(3/7)	---	
Underline Disease				
Diabetes Mellitus	10(7/4)	7(6/4)	3(11/5)	0.229
Hypertension	10(7/4)	7(6/4)	3(11/5)	
Ischemic Heart Disease	17(12/6)	17(15/6)	0	
Others	6(4/4)	5(4/6)	1(3/8)	
HIV status				
Positive	17(12/6)	17(12/6)	0	0.093
Viral Hepatitis				
B&C	22(16/3)	21(19/3)	1(3/8)	0.056
HCV	19(14/1)	19(17.4)	---	
HBV	6(4/4)	5(4/6)	1(3/8)	
Out Come				
Cure	117(86/7)	96(88/1)	21(80/8)	0.098
Complete treatment	---	---	---	
Failure of treatment	1(0.7)	---	1(3/8)	
Default	11(8/1)	7(6/4)	4(15/4)	
Transfer out	1(0/7)	1(0/9)	---	
Death	5(3/7)	5(4/6)	---	
Recurrent DIH	23(17)	19(17/4)	4(15/4)	0.803
Outcome				
Acceptable outcome	116(85/9)	95(87/2)	21(80/8)	0.400
Non-acceptable outcome	19(141)	14(12/8)	5(19/2)	
Total	135	109	26	---

Table 3

Demographic and clinical analysis in recurrence of drug induced hepatitis

Variable	Total Patients No (%)	Re-Hepatitis No (%)	P Value
Sex			
...Male	67(49/6)	8(34/8)	0.118
..Female	68(50/4)	15(65/2)	
Age group			
.. <35	30(22/2)	4(17/4)	0.448
..35-60	49(36/3)	11(47/8)	
..>60	56(41/5)	8(34/8)	
Nationality			
..Iranian	104(77)	19(82/6)	0.738
..Afghani	30(22/2)	4(17/4)	
..Others	1(0.7)	---	
Smoking			
.. Active smoker	42(31/1)	4(17/4)	0.227
.. Passive smoker	8(5/9)	2(8/7)	
.. Non smoker	85(63)	17(73/9)	
Opium consumption	34(25/2)	4(17/4)	0.495
Co-Morbidity			
..Yes	58(51/8)	13(56/5)	0.679
..No	54(48/2)	10(43/5)	
Viral Hepatitis(B&C)	22(16/3)	5(21/7)	0.438
Total	135	23	---