Currently Used Low-Dose Pyrazinamide Does Not Increase Liver-Injury in the First Two Months of Tuberculosis Treatment

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Abstract

Objective In the 1950s, a high-dose (40-70 mg/kg/day) of pyrazinamide (PZA), was reported to cause drug-induced liver injury (DILI) at an unacceptable frequency. It remains unclear whether adding PZA (Z) at the currently accepted low-dose (20-25 mg/kg/day) for two months to a regimen of isoniazid (H) + rifampicin (R) + ethambutol (E) actually increases the risk of DILI.

Method Smear-positive tuberculosis patients were treated with daily HRE or HRZE regimen under direct observation. We used three independent models. Model 1 was analyzed with a multivariate Cox-analysis using a pre-matched cohort. Next, propensity score matching was conducted using the nearest neighbor method with caliper of 0.03. Models 2 and 3 were analyzed by univariate and multivariate Cox-analyses, respectively, with the matched cohort. DILI was assessed based on the guidelines of the American Thoracic Society.

Results We reviewed the records of 383 patents (male, n=260; female n=123; mean age, 64±20 years). Among these patients, 75 patients were treated with HRE and 308 were treated with HRZE. DILI occurred in the first two months in 24% (18/75) and 8% (24/308) of the HRE-treated and HRZE-treated cases, respectively. In all three of the models, DILI was less frequent in patients treated with the HRZE regimen: Model 1, HR of 0.30 (95% confidence interval (CI) 0.14-0.68, p=0.004); Model 2, HR of 0.37 (95%CI 0.14-0.96, p=0.041); and Model 3, HR of 0.34 (95%CI 0.12-0.94, p=0.038).

Conclusion The addition of the currently accepted low dose (20-25 mg/kg/day) of PZA to the HRE regimen did not increase the incidence of DILI during the first two months of treatment.

Key words: propensity score, side effect, pyrazinamide hepatotoxicity, toxicity of tuberculosis medications

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Introduction

Pyrazinamide (PZA), which is currently one of the four first-line anti-tuberculosis agents (1), was reported to cause an unacceptable incidence of drug-induced liver injury (DILI) in the 1950’s. In that era, PZA was prescribed at much higher doses (40-70 mg/kg/day) in comparison to the currently accepted dose (20-25 mg/kg/day) (2). Since the 1970s, many trials have utilized lower doses of PZA to avoid the development of DILI (3-6), and these lower doses have led to satisfactory bactericidal effects and a low incidence of DILI. Since then, no studies have thoroughly evaluated whether the addition of low-dose PZA to other drugs actually increases the risk of DILI. The isoniazid + rifampicin + ethambutol + pyrazinamide (HRZE) regimen appears to be superior to the isoniazid + rifampicin + ethambutol (HRE) regimen for eradicating tuberculosis (1, 4, 5). Nevertheless, HRE is still the preferred regimen over HRZE during the first two months of treatment for pa-

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tients who are considered to be at a high risk of DILI (1, 7). Despite the distinctive presentation of side effects (hepatotoxicity with isoniazid, high bilirubin and alkaline phosphatase with rifampicin, and highly elevated aminotransferase level with PZA) (7), it is practically difficult to identify the causative agent for DILI when using a combination therapy. In particular, it is difficult to determine whether PZA actually causes DILI. The aim of the present study was to determine whether an HRZE regimen actually causes a higher incidence of DILI in comparison to an HRE regimen.

Materials and Methods

In a recent study, we reported that decreased activity in daily living was a serious risk factor for the development of anti-tuberculosis DILI (8). In the same study, we also reported that patients treated with HRZE exhibited a lower, but non-significant, incidence of DILI in comparison to those treated with HRE. In the present study, we conducted an additional analysis that included data from recently hospitalized patients. This analysis was performed to evaluate the impact of the addition of PZA to an HRE regimen on the incidence of DILI during the first two months of anti-tuberculosis treatment. Three independent models were used to investigate the impact of PZA. Model 1 was analyzed by a multivariate Cox-analysis with a pre-matching cohort. Prior to the analyses of Model 2 and Model 3, propensity score matching was conducted. Models 2 and 3 were analyzed by a univariate Cox-analysis and a multivariate Cox analysis, respectively using the matched cohort.

This study was approved by the Institutional Review Board of Yokohama City University Hospital and the Institutional Review Board of Fukujuji Hospital. These boards waived the requirement for informed consent because of the retrospective nature of this study and because the patients’ anonymity was ensured.

Patients

We consecutively reviewed patients admitted to the isolation ward with a primary diagnosis of pulmonary tuberculosis. According to the patients’ admission date, we reviewed the records of patients admitted to Yokohama City University, Yokohama, Japan, from January 2007 to September 2012, and those admitted to Fukujuji Hospital, Tokyo, Japan, from January 2009 to December 2009. The inclusion criteria were as follows: (i) a diagnosis of active smear-positive pulmonary tuberculosis; (ii) the patient was newly diagnosed with the disease; (iii) ≥20 years of age; (iv) the daily administration of HRE or HRZE as the initial treatment regimen; (v) the patient’s tuberculosis was not resistant to any of the four drugs; and (vi) the patient was human immunodeficiency virus (HIV) negative.

The patients who satisfied the inclusion criteria constituted the pre-matching cohort. Some of the pre-matching cohort patients who could not be matched through propensity-score matching constituted a matched cohort.

Treatments

One of the following two daily combination regimens was administered to each patient for the first two months, under direct observation: (i) HRZE, which was composed of isoniazid (5 mg/kg/day, 7 days/week, maximum dose 300 mg/day), rifampicin (10 mg/kg/day, 7 days/week, maximum dose 600 mg/day), PZA (25 mg/kg/day, 7 days/week, maximum dose 1,500 mg/day), and ethambutol (15-20 mg/kg/day, 7 days/week, maximum dose 1,000 mg/day) for two months followed by the administration of isoniazid and rifampicin at the same dosage for four months; or (ii) HRE at the same dosages for two months followed by the administration of isoniazid and rifampicin at the same dosages for seven months (1). Although some other regimen options were also recommended (1), the two regimens above were most commonly used in our hospitals when the bacilli did not display resistance to any of the regimen compounds. Patients treated with other regimens were excluded from the study.

Outcomes

PZA was only prescribed for the first two months of the combination therapy. To assess the impact of PZA, we therefore focused on DILI that occurred in the first two months.

DILI is ultimately a clinical diagnosis. Preferably, it should be evaluated with histologic specimens of the liver; however, in practice, this is not feasible for most active tuberculosis cases. For the current study, we defined DILI as a liver injury for which the American Thoracic Society guidelines recommends the withholding anti-tuberculosis treatment due to the substantial risk of the development of an irreversible liver injury (7). The current guidelines recommend the withholding of all ongoing anti-tuberculosis medications in cases with the following criteria: an elevation of serum aminotransferase concentrations to ≥ three times the upper limit of the normal range (120 IU/L) along with the presence of jaundice and/or symptoms of hepatitis, or an elevation of serum aminotransferase concentration to ≥ five times the upper limit of the normal range (200 IU/L) regardless of the presence of jaundice and/or symptoms of hepatitis (7). All physicians in our hospitals used the same criteria. Once a patient satisfied the criteria above, all anti-tuberculosis medication was withheld. Re-challenge with anti-tuberculosis medications was decided according to the American Thoracic Society Drug-induced Liver Injury (ATS DILI) guideline (7).

A slight elevation of aminotransferase without a change of or withdrawal of the treatment regimen, was not regarded as DILI for the purposes of this study. The patients were under close observation in the first two months and blood tests, including blood cell counts, and the evaluation of aminotransferase, total bilirubin and electrolyte levels were performed once or twice a week.
Statistics

Propensity score matching using the nearest neighbor method with a caliper of 0.03 was performed to make balanced pairs based on the baseline characteristics at admission (9-12). For the propensity score matching, one HRE-treated patient was matched with four HRZE-treated patients. The value of aspartate aminotransferase (AST) was expressed as a binary variable with a cutoff value of average (≥37 IU/L) throughout the multivariate analyses, because the value was strongly skewed and did not display normal distribution. Alanine aminotransferase (ALT) was not adopted for the multivariate analysis due to its possible multi-colinearity with AST. Hepatitis C virus (HCV) infection was not used for the multivariate Cox model in Model 3, because few patients in the matched cohort had HCV infection. The other co-variables were used for the multivariate Cox analysis in Model 1 and 3 and for the propensity score matching. Cases that were discharged alive or who died in the hospital were censored in the Cox model. The Wilcoxon rank sum test and Fisher’s exact test were used to compare the baseline characteristics between the cohorts treated with HRZE and HRE. A significance level of 0.05 was adopted throughout the study. In the present study, the “±” sign represents the standard deviation, and not the standard error. The data analyses were performed using the Excel Toukei 2012 (SSRI, Tokyo, Japan) and GraphPad Prism ver. 5.04 software programs (GraphPad Software, San Diego, USA).

Results

Patient background characteristics

We reviewed the records of 383 patients (male, n=260; female n=123; mean age, 64±20 years). Among these patients, 308 patients were treated with HRZE and 75 patients were treated with HRE (Table 1). The study population included many elderly patients and patients with decreased activity of daily living. There were a very limited number of HIV-positive tuberculosis cases in our hospitals. These patients were excluded from the analysis. It is known that the epidemiology of tuberculosis varies depending on the area and country. Our cohort well-reflected the Asian or Japanese epidemiology (13). As expected, the patients treated with the HRE regimen tended to be prescribed for patients who exhibited the following characteristics: higher age, liver disease, elevated AST level, or decreased activity of daily living as determined by a Barthel Index (14) value of 0–100, in which 100 indicates the best activity level.

Side effects and drug interruption

Among the 75 HRE-treated cases, anti-tuberculosis treatment was interrupted for 22 (29%) cases for the following reasons; 18 patients experienced a DILI in the first two months of treatment, three experienced drug-induced rashes, and one had a drug-induced fever. Among the 308 HRZE-treated cases, anti-tuberculosis treatment was interrupted for 61 (20%) cases for the following reasons; 24 patients experienced a DILI in the first two months, three patients experienced drug-induced rashes, four patients experienced drug-induced fevers, four patients experienced concomitant drug-induced rashes and fevers, three patients had difficulties with oral administration, two patients experienced drug-induced thrombopenia, and one patient had drug-induced gout. Among the patients with DILI, seven HRE-treated patients and five HRZE-treated patients died.

Three of the 18 HCV infected patients developed a DILI in the first two months.

On average, the 18 patients who developed a DILI due to the HRE regimen had an AST level of 200±169 IU/L, an
2.3±1.5 mg/dL at diagnosis. The 24 patients who had DILI, an ALT level of 140±167 IU/L, and a total bilirubin level of 35.0mg/dL at diagnosis, had a total bilirubin level of 0.8±0.5 mg/dL, at diagnosis (Table 2). The Wilcoxon rank sum test indicated that these values did not differ between two groups with p values of 0.446, 0.055, 0.073, and 0.174 for AST, ALT, total bilirubin, and alkaline phosphatase, respectively.

### Table 2. The Laboratory Data at DILI Diagnosis.

| Treatment regimen | HRE | HRZE | Number of patients | 18 | 24 |
|-------------------|-----|------|--------------------|----|----|
| AST (IU/L)        | 200±169 | 292±283 |                |    |    |
| ALT (IU/L)        | 140±167 | 222±226 |                |    |    |
| Total bilirubin (mg/dL) | 2.3±1.5 | 1.7±1.7 |                |    |    |
| Alkaline phosphatase (IU/L) | 677±585 | 477±271 |                |    |    |
| AST and/or ALT ≥ 200 (IU/L) | 12 (67%) | 18 (75%) |                |    |    |
| AST: aspartate aminotransferase | | |                |    |    |
| ALT: alanine aminotransferase | | |                |    |    |
| HRE: isoniazid + rifampicin + ethambutol | | |                |    |    |
| HRZE: isoniazid + rifampicin + pyrazinamide + ethambutol | | |                |    |    |

### Evaluating the risk of DILI with the HRE and the HRZE regimens

Model 1: The multivariate Cox model, which was adjusted for 13 other co-variables in the pre-matching cohort provided an HR of 0.30 (95%CI 0.14-0.68, p=0.004) (Table 3).

Propensity score matching: The propensity score was generated with a logistic regression analysis. In the logistic regression analysis, age and serum creatinine level were significantly associated with regimen choice. Propensity score matching was conducted. The matched cohort consisted of 35 HRE-treated patients and 140 HRZE-treated patients. In this matched cohort, no variables differed between the HRE-treated and HRZE-treated patients (Table 4).

Model 2: The univariate Cox model in the matched cohort provided an HR of 0.37 (95%CI 0.14-0.96, p=0.041) (Table 3). The Kaplan-Meier curves are presented in Figure. A log-rank test revealed that DILI was more frequent in the HRZE-treated patients (p=0.032).

Model 3: The multivariate Cox model, which was adjusted for 12 other co-variables in the matched cohort provided an HR of 0.34 (95%CI 0.12-0.94, p=0.038) (Table 3).

### Discussion

We performed an observational study to compare the risks of DILI between patients treated with the HRE and HRZE regimens using propensity score and Cox models. Our cohort included many elderly patients, many patients with low activity of daily living, no HIV-positive patients, and no patients with drug-resistant tuberculosis. The three independent models consistently indicated that the HRZE regimen was associated with a lower risk of DILI in the first two months. It indicated that the addition of a currently accepted low-dose (20-25 mg/kg/day) of PZA to the HRE regimen did not increase the incidence of DILI during the first two months of treatment. Even though a high-dose (40-70 mg/kg/day) of PZA has been found to be associated with a high frequency treated and HRZE-treated patients (Table 4).

### Table 3. Risk of Drug-induced Liver Injury in Three Independent Models.

| Model | Propensity score matched? | Number of cases HRE/HRZE | Adjusted for other variables? | Hazard ratio (95%CI, p value) |
|-------|---------------------------|--------------------------|------------------------------|-----------------------------|
| 1     | No                        | 75/308                   | Yes                          | 0.30 (0.14-0.68, 0.004)     |
| 2     | Yes                       | 35/140                   | No                           | 0.37 (0.14-0.96, 0.041)     |
| 3     | Yes                       | 35/140                   | Yes                          | 0.34 (0.12-0.94, 0.038)     |

HRE: isoniazid + rifampicin + ethambutol
HRZE: isoniazid + rifampicin + pyrazinamide + ethambutol
95%CI: 95% confidence interval

The following variables were adjusted for Models 1 and 3: Age, sex, albumin, hemoglobin, aspartate aminotransferase (≥ 37 IU/L), alkaline phosphatase, total bilirubin, LDH, creatinine, habitual drinker, Barthel Index, and liver disease. Hepatitis C virus was adjusted only for Model 1.

### Figure

A Kaplan-Meier curve for drug-induced liver injury (DILI) in a propensity-score matched cohort. HRZE: isoniazid + rifampicin + pyrazinamide + ethambutol, HRE: isoniazid + rifampicin + ethambutol.

ALT level of 140±167 IU/L, and a total bilirubin level of 2.3±1.5 mg/dL at diagnosis. The 24 patients who had DILI due to the HRZE regimen had an ALT level of 292±283 IU/L, an ALT level of 222±226 IU/L, and a total bilirubin level of 1.7±1.7 mg/dL, at diagnosis (Table 2). The Wilcoxon rank sum test indicated that these values did not differ between two groups with p values of 0.446, 0.055, 0.073, and 0.174 for AST, ALT, total bilirubin, and alkaline phosphatase, respectively.

### Table 4. The Characteristics of the Patients’ Characteristics in the Matched Cohort.

|                | HRE | HRZE | p   |
|----------------|-----|------|-----|
| N              | 35  | 140  |     |
| Age (year)     | 74±16 | 72±14 | 0.087|
| Sex (female)   | 8 (23%) | 49 (35%) | 0.227|
| Albumin (g/dL)| 2.9±0.8 | 2.9±0.7 | 0.688|
| Hemoglobin (g/dL)| 11.0±1.9 | 11.0±1.7 | 0.939|
| Aspartate aminotransferase (IU/L) | 35±20 | 40±50 | 0.450|
| Alanine aminotransferase (IU/L) | 27±23 | 31±41 | 0.620|
| Aspartate aminotransferase ≥ 37 IU/L | 11 (31%) | 46 (33%) | 1.000|
| Alkaline phosphatase (IU/L) | 335±192 | 342±199 | 0.718|
| Total bilirubin (mg/dL) | 0.8±0.5 | 0.8±0.8 | 0.281|
| LDH (IU/L)     | 241±104 | 234±88 | 0.935|
| Cr (mg/dL)     | 0.8±0.5 | 0.9±0.8 | 0.978|
| Habitual drinker (≥ 3 days) | 6 (17%) | 28 (20%) | 0.814|
| Barthel Index  | 49±43 | 58±42 | 0.267|
| Hepatitis C virus infection | 0 (0%) | 4 (2.9%) | 0.581|
| Liver disease  | 1 (2.9%) | 8 (5.7%) | 0.690|

HRE: isoniazid + rifampicin + ethambutol
HRZE: isoniazid + rifampicin + pyrazinamide + ethambutol
The Barthel Index is a scale for the activities of daily living with range of 0–100, wherein 100 indicates the best activity level.

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Table 5. Randomized Controlled Trials Comparing the Incidence of Drug-induced Liver Injury (DILI) Due to Regimens with and without Pyrazinamide since 1980.

| Study                                      | Regimen | Incidence of DILI |
|--------------------------------------------|---------|-------------------|
| British Thoracic Association, 1981          |         |                   |
| 1.5 g (weight <50 kg) or 2.0 g (weight 50-74 kg) or 2.5 g (weight ≥75 kg); a day. | 0%       |                   |
| Persistently abnormal liver function tests which justified the cessation of the prescribed chemotherapy, either temporarily or permanently. |          |                   |
| 2HRZE + 4HR, 3/164 (1.8%); 2HRE + 7HR, 6/177 (3.4%). |          |                   |
| Hong Kong Chest Service/British Medical Research Council, 1982 |         |                   |
| 2.0 g (weight <50 kg) or 2.5 g (weight ≥50 kg); 3 times a week. | 0%       |                   |
| Abnormalities found in the liver function test leading to a modification to the regimen. 6HRSZE3, 3/244 (1.3%); 6HRSE3 0/234 (0.0%). |          |                   |
| Chang et al. conducted cohort and nested case-control analyses. The study, which defined hepatotoxicity as a serum alanine transaminase level of more than three times the upper limit of normal from 12 or more weeks after the initiation of treatment, concluded that the addition of pyrazinamide to isoniazid and rifampin increased the risk of hepatotoxicity (15). This does not conflict with our results as the study by Chang et al. was concerned hepatotoxicity from 12 or more weeks after the start of treatment, while we focused on DILI in the first two months of the treatment. Durand et al. reported the prognosis of 18 patients with fulminant or subfulminant liver failure due to the administration of antituberculosis medications. Nine of the 18 patients were treated without PZA, and nine were treated with a PZA-containing regimen. The PZA cases demonstrated a higher level of mortality and more frequently required liver transplantation. However, the study did not mention the frequency of DILI (16). In our clinical experience, PZA cases with DILI often have highly elevated AST and/or ALT (>1,000 IU/L). We agree with Durand et al. that DILI caused by PZA may be critical in some cases, thus it is crucial to perform periodic blood tests to monitor liver function (7). Interestingly, in the Durand et al. study, nine non-PZA cases presented jaundice after a shorter duration of treatment (range 5-85 days, median 7 days, average 16 days) than the nine PZA cases (range 7-244 days, median 51 days, average 67 days) (16). This result, together with the study by Chang et al., and the results of our own study, supports the current guideline that recommends the cessation of PZA after two months of treatment to minimize the risk of DILI, once drug... |
susceptibility is confirmed (1).

It appears paradoxical that the addition of PZA, a hepatotoxic agent, to other drugs could be related to a lower incidence of DILI in the first two months. One possible explanation is that PZA decreases the serum concentration of rifampicin. Grosset et al. suggested that it was very likely that a pharmacological interaction occurred among anti-tuberculosis medications (17). Immanuel et al. revealed that the bioavailability of rifampicin was reduced by the concomitant administration of other anti-tuberculosis medications (18). In 1992, Dickinson et al. administered rifampicin-alone or a rifampicin + PZA regimen to mice and demonstrated that the serum rifampicin concentration was 30% lower in the rifampicin + PZA group (19). The following year, Jain et al. conducted a small randomized trial in human patients to compare a rifampicin + isoniazid regimen and a rifampicin + isoniazid + PZA regimen. Jain et al. concluded that the concomitant administration of PZA also decreased the concentration of rifampicin in humans (20). This finding is not considered in the current tuberculosis guideline (1).

Our study is associated with some limitations. First, because of the retrospective nature of the study design and the number of patients assessed, we should not prematurely conclude that PZA prevents DILI. This potentially preventative effect should be evaluated further in a prospective study. Second, we should be careful when applying the results of the present study, concerning the use of PZA, to HIV-positive patients and patients with liver disease, as our cohort did not include any (or very few) of such patients.

Conclusion

In contrast to previous expectations, the addition of the currently accepted low dose (20-25 mg/kg/day) of PZA to the HRE regimen did not increase the incidence of DILI during the first two months of treatment. This is probably because PZA decreased the serum concentration of rifampicin (17-20). PZA can be tolerated by the majority of patients with active tuberculosis, including elderly patients, but patients who are at an increased risk of DILI need to be identified and closely monitored so that changes in management can be instituted quickly to prevent mortality. The HRZE regimen was superior to the HRE regimen for eradicating tuberculosis. We are therefore of the opinion that there is little reason to avoid the HRZE regimen for fear of DILI in HIV-negative tuberculosis patients.

The authors state that they have no Conflict of Interest (COI).

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