J Infect Chemother 25 (2019) 1026–1030

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Safety of pyrazinamide-including regimen in late elderly patients with pulmonary tuberculosis: A prospective randomized open-label study☆

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ARTICLE INFO

Article history:
Received 10 November 2018
Received in revised form
22 May 2019
Accepted 29 May 2019
Available online 19 June 2019

Keywords:
Tuberculosis
Pyrazinamide
Late elderly patients
Liver injury

ABSTRACT

Pyrazinamide (PZA) -including regimen had not been fully recommended for late elderly patients with tuberculosis (TB) by Japanese Society for Tuberculosis until 2018. Studies on the safety of adding PZA to other first-line TB drugs for late elderly patients are limited. In this prospective randomized open-label study, we aimed to assess the safety of regimen including PZA for patients aged 80 or older.

Patients in their eighties with smear-positive pulmonary TB without any liver diseases were randomly assigned to HRE (isoniazid, rifampicin, ethambutol) group or HREZ (HRE and PZA) group. The primary endpoint was discontinuation or interruption rate of treatment due to liver injury. Other endpoint included overall rate of liver injury, time to culture conversion, and overall mortality.

Eighty-nine patients were assigned to either HRE group (n = 45) or HREZ group (n = 44). Clinical background was not different in two groups including age, smear grade, body weight, serum albumin, and activity degree. Discontinuation of treatment due to liver injury occurred in 15.6% of HRE group and 9.1% of HREZ group, which showed no statistical difference. Incidence of liver injury was also comparable between two groups. Overall mortality was statistically higher in HREZ group (3 in HRE vs. 10 in HREZ), although all deaths seemed to be irrelevant to PZA use. Time to culture conversion was significantly shorter in HREZ group (43.6 days vs. 30.2 days).

In conclusion, regimen including PZA seems to be safe for late elderly patients with pulmonary TB.

1. Introduction

Pyrazinamide (PZA) is a first-line drug in anti-tuberculosis (TB) treatment together with isoniazid (INH), rifampicin (RFP), and ethambutol (EB) [1]. However, Japanese guideline had long been recommending careful consideration for using PZA in late elderly patients aged 80 or older. The guideline could be read as suggesting that general principle is to avoid using PZA for those patients. Official clinical guideline from American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America also says that the benefit of including PZA in the initial regimen for elderly patients with modest disease and low risk of drug resistance may be overweighed by the risk of serious adverse events [2]. Consequently, not a few experts have been avoiding the use of PZA during the intensive phase among patients over 75 years of age even in other countries. In January 2018, Japanese Society for Tuberculosis finally published the official proposal on the indication of regimen with PZA for patients over 80 years old to revise the guideline by deleting the recommendation of avoiding PZA for these patients [3]. However, only limited studies are available on the safety and tolerability of PZA-including regimen in late elderly patients. A retrospective study reported that liver injury was more frequent in elderly patients than younger patients [4], while another reported no difference between ages [5]. PZA-including regimen were reportedly more often associated with drug-induced liver injury than non-including regimen not in all-age patients [6] but in elderly patients [7]. Another study reported that PZA-including regimen did not increase liver injury even in elderly patients [8].

However, all these findings were from retrospective studies and no studies have ever been prospectively conducted on the safety of adding PZA for late elderly patients. In this prospective randomized

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https://doi.org/10.1016/j.jiac.2019.05.030
1341-321X/

open-label study, we aimed to assess the safely of PZA-including regimen for TB patients aged 80 or older.

2. Patients and methods

2.1. Study subjects

This study was conducted in accordance with good clinical practice and the ethical principles outlined in the Declaration of Helsinki. The protocol was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center on March 2015 (KCRC-26-37). All patients provided written informed consent before entering the study.

Patients eligible for inclusion were smear-positive pulmonary TB inpatients aged 80–89 years in our hospital. Exclusion criteria included: either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) over 100, positive for either hepatitis B antigen or hepatitis C antibody, history of liver cirrhosis, hepatitis or other liver diseases, history of heavy alcohol drinking habit, patients from whom written informed consent was not provided, patients who were unable to take medicine orally or via nasogastric tube or patients who were thought to be better to receive intravenous drugs by an attending physician.

2.2. Study design

This study was a prospective, randomized, open-label, single-center study. On the admission day in our hospital ward of TB, patients were randomly assigned to either HRE (INH, RFP, EB) group or HREZ (HRE and PZA) group. Dose of drugs were as follows: INH 5 mg/kg (max 300 mg), RFP 10 mg/kg (max 600 mg), EB 15 mg/kg (max 750 mg), PZA 25 mg/kg (max 1500 mg) to omit fractions. In HRE group, all three drugs were given for two months followed by 7-month HR. In HREZ group, all four drugs were given for two months followed by 4-month HR, as indicated in the Japanese guideline. Blood test and sputum culture were conducted at least every two weeks. Sputum culture was conducted with solid media. Activity degree of daily life was assessed at the time of admission and defined as follows: 1; walk alone without aid/help, 2; need walking aid/help, 3; need wheelchair propelled by others, 4; being on bed all day.

2.3. Endpoints

The primary endpoint was the discontinuation or interruption rate of treatment due to liver injury. The standard values for discontinuing treatment were as follows: AST or ALT above 5-fold upper limit of the institutional standard levels, or above 3-fold upper limit with symptoms suggesting hepatitis such as fatigue, nausea, or appetite loss. Other endpoint included overall rate of liver injury, time to culture conversion, and mortality from all causes. Overall rate of liver injury was defined on the basis of the Criteria for safety evaluation of antimicrobial agents published by Japanese Society of Chemotherapy in 2011 in which increase of liver aminotransferases above 2.5-fold of the upper limit of the institutional standard levels was defined as adverse event [9]. The increase of liver aminotransferases due to heart failure just before dying after discontinuing TB treatment was not classified as liver injury. Time to culture conversion was defined as number of days from initiating treatment to the first day of at least twice consecutive negative culture. Mortality from all causes included events during treatment as outpatients in our hospital clinic after discharge.

2.4. Statistical analysis

To determine the sample size of the study, we assumed discontinuation rate of treatment due to liver injury for 20% in late elderly patients. With a two-sided alpha level of 0.05, non-inferiority margin as 0.2, a total enrollment of 100 patients was needed to attain a power of 80%. Thus, the target sample size was determined as 100. However, as the study period was over before reaching 100, total number of recruited patients ended with 90, resulting in a power of 76%. Safety was assessed among all allocated patients. Data were expressed as number of patients or as mean with standard deviation. Numerical data were compared using the Student's t-test or Mann-Whitney's *U* test, and categorical variables were compared using the Chi-squared test or Fisher's exact test. Ranked values such as smear grade and activity degree of daily life were compared with Mann-Whitney's U test. Time to culture conversion was compared using the Mann-Whitney's U test. A p value of <0.05 was considered to be significant. Analyses were performed using SPSS software version 18.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Baseline characteristics

Ninety patients in their eighties were recruited for candidates between April 2015 and March 2018 and provided written informed consent. One participant was found not to have met the entry criteria and was not included in the study. Finally, eighty-nine patients were enrolled: 45 patients were assigned to receive HRE, and 44 patients to receive HREZ. As shown in Table 1, there were no differences in baseline characteristics between HRE and HREZ group. Serum albumin level tended to be higher in HRE group but without statistical significance. One patient in HREZ group was found to show low-level INH resistance (0.2 μg/ml in solid media), and one month after the treatment initiation levofloxacin was added to the treatment.

3.2. Primary outcome

Outcomes were assessed in 89 patients. Discontinuation of treatment from all causes occurred in 15 of 45 patients in HRE group and 16 of 44 in HREZ group with no statistical difference ($p = 0.764$) (Fig. 1). Overall discontinuation rate was as high as

Table 1
Baseline clinical characteristics.

	HRE group	HREZ group	*p* value
Number of patients	45	44	
Male: Female	22 : 23	28 : 16	0.161
Age, years	84.3 ± 2.8	84.7 ± 3.1	0.532
Body weight, kg	46.3 ± 10.8	49.4 ± 8.8	0.196
unable to be measured, n	8	9	0.748
Smear grade, Gaffky scale	5.5 ± 3.1	5.5 ± 3.2	0.555
Serum albumin, g/dl	3.0 ± 0.7	2.7 ± 0.8	0.094
Activity degree, 1–4[a]	2.4 ± 1.2	2.7 ± 1.2	0.524
Prior liver function over UNL[b]	13	16	0.452
Drug resistance	EB 1	EB 1[c] INH 1[c]	

Data were expressed as number of patients or as mean with standard deviation.
EB: ethambutol, INH: isoniazid, UNL: upper normal limit of the institutional standard level.

[a] Activity degree of daily life was assessed as described in the methods section. Briefly, 1: walk alone, 2: need walking aid/help, 3: need wheelchair, 4: on bed all day.

[b] Number of patients with liver aminotransferase over upper normal limit before treatment.

[c] Separate individuals, INH resistance with low-level (0.2 μg/ml in solid media).

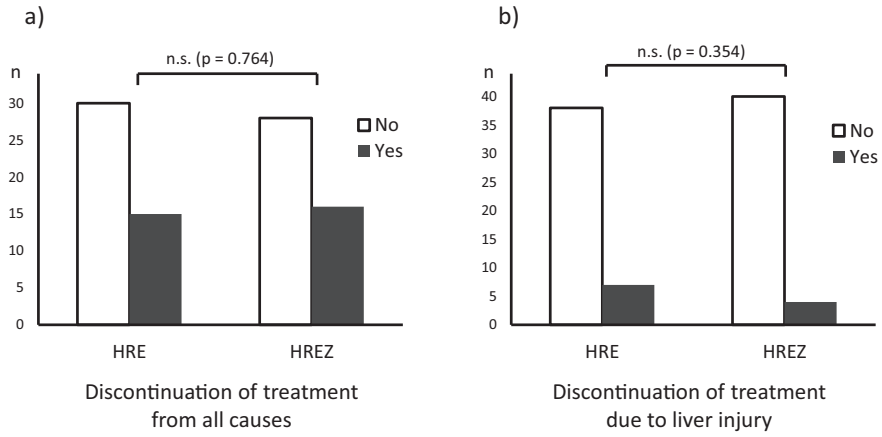

Fig. 1. Discontinuation of treatment from all causes (a) and due to liver injury (b). Number of patients were shown in each chart. No differences were found between two groups in both charts.

34.8%. Discontinuation of treatment due to liver injury, defined as a primary outcome, occurred in 7 of 45 patients in HRE group (15.6%) and 4 of 44 in HREZ group (9.1%), which was not statistically significant ($p = 0.354$).

Causative drugs for liver injury resulting in treatment discontinuation varied among 11 patients: INH for two, RFP for one, PZA for two, INH or PZA for one, INH or RFP for one, other antimicrobial agent for one, unknown for two, and liver metastasis of abdominal cancer for one. Of those 11 patients, 6 patients had elevated levels of AST/ALT within the inclusion criteria before treatment initiation, which was more frequent than expected number 3.3 from total population. Moreover, body weight was unable to be measured in four of 11 patients, which was also almost twice as frequent as in total population.

All patients but one who discontinued treatment due to liver injury recovered their liver function only by withdrawing from TB treatment, with maximum AST/ALT under 300. Only one patient suffered from liver injury with AST over 800, but also recovered by withdrawing all HREZ drugs with suspected causative drugs as PZA or INH. He was resigned to receive PZA and underwent desensitization of INH successfully.

3.3. Secondary outcome

Secondary outcome was also assessed in 89 patients (Table 2). Elevated levels of AST/ALT over upper normal limit were found in 47 patients, including 27 with elevated levels of those enzymes before treatment initiation. Most of these abnormalities returned to normal or remained stable without any changes of treatment. Elevated levels of AST/ALT over 2.5-fold of upper limit, defined as liver injury on the basis of the Criteria for safety evaluation of antimicrobial agents published by Japanese Society of Chemotherapy in 2011, occurred in 18 patients (20.2%). The occurrence rate of these abnormalities was not different between HRE and HREZ group (17.8% vs. 22.7%). All adverse events relating TB drugs, including liver injury, were also found almost equally in these two groups.

Time to culture conversion to negative was shorter in HREZ group (30.2 ± 17.3 days) than HRE group (43.6 ± 27.5 days) with statistical significance ($p = 0.013$). Overall mortality from all causes was significantly higher in HREZ groups, although all deaths seemed to be irrelevant to PZA use.

3.4. Clinical characteristics of patients who died

Overall mortality from all causes during treatment was 14.6% and all deaths were investigated in detail (Table 3). Eight of 13 patients died from aspiration pneumonia and/or heart failure. Two died from malignant diseases and one each from massive hemoptysis, brain attack, and unknown cause of sudden death. Among 13 patients, liver injury over 2.5-fold of upper limit occurred in two patients in HRE group and four in HREZ group. Two patients each in both groups were obliged to discontinue the treatment due to liver injury.

4. Discussion

In this prospective randomized study, we showed that the discontinuation rate of TB treatment due to liver injury, defined as the primary endpoint, was not higher in patients aged 80 to 89 with PZA-including regimen. Significant differences were neither found in the rate of liver injury between the groups. Time to culture conversion was significantly shorter with PZA-including regimen. Although overall mortality was higher in PZA-including regimen group, all deaths seemed to be irrelevant to PZA use. The present study suggests that the regimen including PZA seems to be safe for late elderly patients at least in terms of hepatotoxicity.

Overall discontinuation rate of treatment was as high as 34.8%. We previously reported that treatment discontinuation occurred in 31.0% of elderly patients at the age of 70 or older [10] or 21.5% of all-age patients [11]. Considering that the patient population in the present study was older than those, the discontinuation rate in the present study seems reasonable [12].

No difference was observed in the occurrence rate of liver injury between groups with or without PZA. This result was well compatible with previous reports [8,13,14]. Among patients who discontinued TB treatment due to liver injury, there seemed tendency to have elevated levels over upper limit of AST/ALT at

Table 2
Secondary outcome.

	HRE group	HREZ group	*p* value
Number of patients	45	44	
Liver injury UNL 1 <	21	26	0.240
Liver injury UNL 2.5 <	8	10	0.561
All adverse events relating TB drugs[a]	23	24	0.746
All-cause mortality	3	10	0.032
Time to culture conversion[b], days	43.6 ± 27.5	30.2 ± 17.3	0.013

Data were expressed as number of patients or as mean with standard deviation.
UNL: upper normal limit of the institutional standard level.
[a] All adverse events include liver injury over 2.5 UNL.
[b] Days from treatment initiation to the first day of at least twice negative culture.

Table 3
Clinical features of thirteen patients who died during treatment.

Age	Sex	Group	Activity degree	Body weight	Serum Albumin	Prior liver function UNL 1 <	Liver injury UNL 2.5 <	Discontinuation due to liver injury	Days to death	Cause of death
86	F	HRE	2	44.4	3.7	+	−	−	17	Heart failure with aspiration pneumonia
83	F	HRE	4	ND	1.7	−	+	+	147	Unknown sudden death
80	F	HRE	2	74.5	3.9	−	+	+	180 <	Abdominal cancer
81	M	HREZ	4	48.0	2.3	+	+	+	13	Brain attack
86	F	HREZ	4	51.0	1.9	−	−	−	27	Aspiration pneumonia with heart failure
89	M	HREZ	4	ND	1.4	+	−	−	27	Aspiration pneumonia
89	M	HREZ	2	55.2	2.8	+	−	−	36	Heart failure
86	F	HREZ	2	52.0	3.0	−	−	−	45	Massive hemoptysis
88	M	HREZ	4	ND	2.1	+	+	+	54	Aspiration pneumonia
88	M	HREZ	4	51.9	1.9	−	+	−	88	Aspiration pneumonia
80	F	HREZ	4	ND	2.3	+	−	−	90	Aspiration pneumonia
85	M	HREZ	4	42.0	2.0	−	−	−	100	Aspiration pneumonia
80	M	HREZ	4	ND	2.4	−	+	−	138	Abdominal Cancer

ND: not determined, all due to disability of standing.
Activity degree of daily life was assessed as described in the methods section.
Days to death: days from the group assignment to death.

baseline, and to be unable to measure their body weight at admission because of disability of standing even with assistance. These were also compatible with previous reports [15,16], although investigating the characteristics of patients who develop liver injury was beyond the scope of the present study.

PZA-including regimen occasionally induce severe hepatotoxicity [17], which occurred in one patient in the present study. However, he recovered soon after withdrawing all four drugs without serious outcome. In agreement with a previous report [5], the present study confirmed that hepatotoxicity induced by PZA is not severer or more uncontrollable than those induced by other TB drugs.

Overall rate of adverse events relating TB drugs did not differ either in both groups. Mortality rate from all causes was as low as 14.6%. This rate was lower than those of previous reports [18–20]. The reason for this lower rate may be attributable to our entry criteria to include only patients who seemed to be able to ingest medicines at admission, although not a few patients underwent nasogastric tube insertion in a short time.

The most major concern in our results would be a higher mortality rate in PZA-including group. We retrospectively investigated each case of death for the details, and found that all deaths were not relevant with PZA use. The main reasons of deaths were aspiration pneumonia and/or heart failure, which were expected to be the general problems in elderly patients. We consider this significant difference may have resulted from a statistical error. In fact, when we conducted the unofficial interim analysis with first 43 allocated patients to judge the validity of proceeding the study, the discontinuation rate due to liver injury was significantly lower, not higher, in PZA-including group (oral presentation in the 2017 Kekkaku annual meeting). This significance turned out to be a statistical error in this final analysis.

The reason for this erroneous result may be explained by the lower tendency of serum albumin level in PZA-including group. Lower level of serum albumin is a well-known predictive factor for death in elderly patients with tuberculosis (TB) [21]. Among patients who died, there was tendency to have elevated levels over upper limit of AST/ALT before treatment initiation, and to be unable to measure their body weight at admission because of disability of standing, and these tendencies were same as found in patients who discontinued treatment due to liver injury. However, again, investigating the characteristics of patients who died was beyond the scope of the present study.

Time to culture conversion to negative was significantly shorter in PZA-including group. This well-established evidence was confirmed to be also adaptable for late-elderly patients in this study. Given that PZA-including regimen is safe in terms of hepatotoxicity in late elderly patients and achieve culture conversion earlier to successfully complete treatment 3 months earlier, this regimen should be considered as a first choice when no other contra-indication exists even in late-elderly patients.

Several limitations of this investigation should be noted. First, because the present study was conducted in a single institution, the results may not be representative of the general population. Second, not all the patients were followed up to the end of treatment because some of them had been transferred to other hospitals after culture conversion. Therefore, all adverse events may not be covered in the present study. In fact, 12 patients in HRE group and 9 patients in HREZ group were transferred to other hospitals after the average of 97.3 days follow-up period in our hospital, although every effort has been made to collect all outcomes. Third, the number of patients included may not have been enough to exclude statistical errors. Although we believe that the higher mortality was irrelevant to the use of PZA, further studies may be necessary to clear this concern.

In conclusion, this prospective randomized open-label study showed that PZA-including HREZ regimen for late elderly patients was as safe as HRE regimen at least in terms of hepatotoxicity. Time to culture conversion was significantly shorter in PZA-including regimen in those patients. This regimen should be considered as a first choice for late elderly patients with no less confidence as well as for younger patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

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