



New Combination for Patients with Latent Tuberculosis Infection: A Pilot Study

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Background: Latent tuberculosis infection (LTBI) is characterized by the presence of immune responses to *Mycobacterium tuberculosis* without clinical evidence of active TB. LTBI treatment among persons at risk for progression to active disease is an important strategy for TB control and elimination. This prospective observational study aimed to compare the incidences of hepatitis and side effects between a new 2-month combination regimen of isoniazid, rifampin and pyrazinamid (2HRZ) plus excipient and the standard 3-month regimen of isoniazid and rifapentine (3HP) for LTBI treatment in Taiwan. **Materials and Methods:** Between January 1, 2017, and December 31, 2017, all patients aged ≥ 20 years diagnosed LTBI were included in the study. Demographic and baseline laboratory assessment of the patients at diagnosis was collected. Eligible individuals were allocated to the 2-month regimen comprising HUEXC030, isoniazid, rifampin, and pyrazinamide (2HRZ) or 3-month regimen with isoniazid and rifapentine (HP). All symptoms and side effects during treatment were recorded. **Results:** Nineteen patients received the 2-month regimen with HRZ plus HUEXC030, while 23 received the 3-month regimen with HP. The treatment completion rates were 73.7% and 82.6% in the 2- and 3-month regimen groups, respectively. The most common side effects during treatment were fatigue/myalgia/weakness, loss of appetite, and rash. The aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels were similar in both groups after 4 weeks of treatment. **Conclusions:** This study demonstrates that LTBI patients receiving the 2-month regimen with HRZ plus HUEXC030 experienced similar side effects including hepatitis as patients on the 3-month regimen with HP. This new combination treatment regimen may be an alternative for the treatment of LTBI.

Key words: Latent tuberculosis infection, isoniazid, pyrazinamide and HUEXC030, isoniazid and rifapentine, rifampin

INTRODUCTION

Tuberculosis (TB) poses a global public health threat and remains one of the major causes of death among infectious diseases.^{1,2} Approximately 10,000–15,000 newly diagnosed TB cases are reported annually in Taiwan. Latent TB infection (LTBI) is characterized by the presence of immune responses to *Mycobacterium tuberculosis* infection without clinical evidence of active TB.³ It is estimated that one-third of the human population harbors TB in its latent form, and from this reservoir, active TB will develop in the coming decades. The likelihood of progression of LTBI to active TB depends on bacterial, host, and environmental factors.⁴ The reactivation of

TB can be averted by preventive treatment. Treatment of LTBI among persons at risk for progression to active disease is an important strategy for TB control and elimination.^{5,6}

There are three major treatment regimens of LTBI according to the treatment guideline in Taiwan. The first regimen comprises 9 months of isoniazid treatment. This treatment duration is longer and results in poor compliance with medication, which directly affects the effectiveness of prophylactic treatment.⁷ Besides, isoniazid therapy also has a high rate of resistance; about 10% of TB cases were resistant to isoniazid in 2000–2010 in Taiwan. Another preventive regimen, comprising 3 months of treatment with isoniazid and rifapentine (HP), has an equivalent efficacy

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to 9 months of isoniazid and fewer side effects but is more expensive.⁸ The Taiwan Centers for Disease Control (CDC) recommends 4 months of rifampin treatment if the index case had multidrug-resistant TB.⁹

A 2-month regimen of isoniazid, rifampin, and pyrazinamide (2HRZ) has been used for LTBI treatment in Portugal for over 20 years. The rationale for the use of HRZ for LTBI treatment is that rifampin and pyrazinamide have good sterilizing capacity and activity against intermittently metabolically active and intracellular organisms. The efficacy of this treatment is equivalent to 9 months of treatment with isoniazid. There is no patient developed disease after completion. However, hepatotoxicity as a side effect is still a major concern.¹⁰ Durate *et al.* found that approximately 1.5% of LTBI patients presented with hepatitis during the 2-month treatment, similar to isoniazid therapy. Adverse events other than hepatotoxicity are similar to isoniazid treatment.

The side effect of hepatitis during 2HRZ treatment is attributed to isoniazid, rifampin, and pyrazinamide. Isoniazid is acetylated by N-acetyltransferase in the liver [Figure 1]. The intermediate by-product of the above process, acetylisoniazid, rapidly hydrolyzes to acetylhydrazine, and is further acetylated by N-acetyltransferase to nontoxic diacetylhydrazine or oxidized to a toxic reactive metabolite by the cytochrome P450 2E1 (CYP2E1) enzyme. This toxic metabolite could be eliminated through glutathione catalysis by glutathione S-transferase. Besides, isoniazid is also hydrolyzed by amidase to toxic hydrazine. Pyrazinamide is metabolized to pyrazinoic acid (PA) by pyrazinamidase in the liver [Figure 2]. Pyrazinamide and PA are further metabolized to 5-hydroxypyrazinamide and 5-hydroxypyrazinoic acid, respectively, by xanthine oxidase. The excipient, HUEXC030 is both a CYP2E1 and amidase inhibitor, and so prevents the metabolism of isoniazid and pyrazinamide to toxic metabolites in the liver, thereby preventing the side effect of hepatitis.

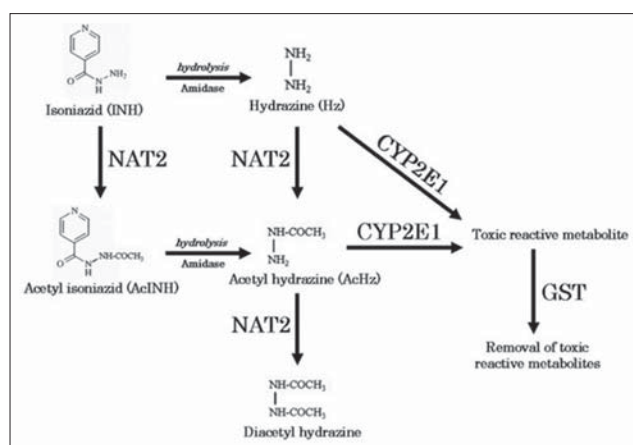


Figure 1: Metabolic pathway of isoniazid in humans

Series animal, pharmacokinetic and pharmacodynamic studies have revealed evidence that this excipient could lessen the incidence of hepatitis resulting from isoniazid and pyrazinamide.¹¹⁻¹³

Most treatment regimens for LTBI have hepatitis as a side effect and involve longer treatment durations. This prospective observational study aimed to compare the incidences of hepatitis and side effects between the new 2-month combination regimen (2HRZ plus excipient) and the standard 3-month regimen comprising isoniazid and rifampine for LTBI treatment in Taiwan.

MATERIALS AND METHODS

This prospective observational study was conducted at Tri-Service General Hospital, a 1700-bed tertiary care center in Taiwan. Patients ≥ 20 years old, who satisfied the inclusion criteria for the diagnosis of LTBI between January 1, 2017, and December 31, 2017, were included in the study. Criteria for participation in the trial included an age of at least 20 years, close contact with TB patients with positive or indeterminate interferon-gamma release assay results without typical TB symptoms, a normal chest radiograph, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels less than the upper limits of normal. Exclusion criteria were as follows: participants with a history of hepatitis B and C or other uncontrollable medical illness; pregnancy; history of allergy to isoniazid, rifampin, and pyrazinamide; history of an acute infectious disease 4 weeks before treatment; and liver function test results higher than the upper limit of normal.

Eligible individuals were allocated to the 2-month regimen with HUEXC030, isoniazid, rifampin, and pyrazinamide or the 3-month regimen with isoniazid and rifampine. Baseline laboratory assessment before treatment included hemogram,

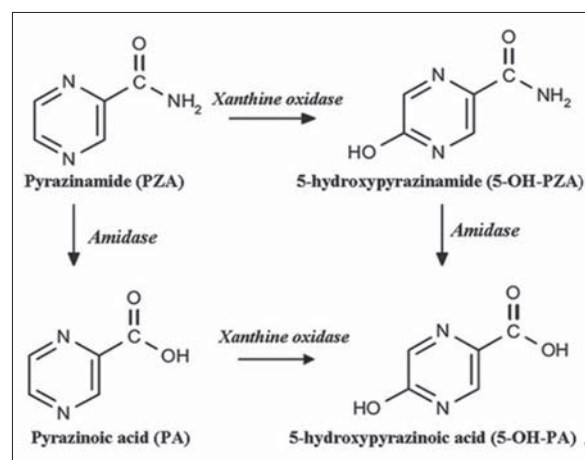


Figure 2: Metabolic pathway of pyrazinamide in humans

serologic markers of hepatitis B and C viruses, and serum biochemistry, including AST, ALT, and total bilirubin and renal function. The study was approved by the Research Ethics Committee of Tri-Service General Hospital (IRB: 2-106-01-008). Individuals in the 2-month regimen group were given isoniazid 5 mg/kg qd, rifampin 10 mg/kg qd, pyrazinamide 20–25 mg/kg qd, and HUEXC030 600 mg qd. Participants in the 3-month regimen group were given isoniazid 15 mg/kg (maximum 900 mg) qw and rifapentine 900 mg qw. The directly observed treatment, short-course strategy was applied to both groups.

A case record form was used to collect information on the demographic and clinical characteristics of the patients at diagnosis. All symptoms and side effects suggestive of drug toxicity (fatigue/myalgia/weakness, headache, nausea/vomiting, fever/chills, rash/itching, and loss of appetite) during the course of treatment were recorded. Serum biochemistry, including AST, ALT, total bilirubin, and renal function were measured after entry and 4 weeks after treatment. Individuals were withdrawn if they experienced intolerable drug side effects (fever, nausea/vomiting, malaise, or hepatotoxicity). Hepatotoxicity was defined as AST or ALT levels five times higher than the upper limit of normal, with or without hepatic symptoms; three times higher than the upper limit of normal with hepatic symptoms; or total bilirubin level higher than 3 mg/dl.

Statistical analysis

Categorical variables were analyzed using Chi-square tests, while continuous variables were compared using the Student's *t*-test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with the SPSS software version (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 42 patients who satisfied the diagnostic criteria for LTBI were included in our study. Comparison of baseline demographic and clinical characteristics of latent TB patients is shown in Table 1. Among them, 19 patients received the 2-month regimen comprising HRZ plus HUEXC030, whereas 23 patients received the 3-month regimen with HP. The mean age of the 2-month treatment group was 51.58 ± 5.14 years, whereas that of the 3-month treatment group was 53.17 ± 3.896 years. The proportion of male individuals in each group was 26.3% and 39.1%, respectively. Hypertensive cardiovascular disease and diabetes were the most common comorbid conditions (19.0%), followed by end-stage renal disease (7.1%). Individuals in the two-month regimen group were given isoniazid 5 mg/kg qd,

rifampin 10 mg/kg qd, pyrazinamide 20–25 mg/kg qd, and HUEXC030 600 mg qd. Participants in the 3-month regimen group were given isoniazid 15 mg/kg (maximum 900 mg) qw and rifapentine 900 mg qw.

Comparison of side effects among LTBI patients receiving 2HRZ plus HUEXC030 and 3HP regimens is shown in Table 2. The treatment completion rate was 73.7% in the 2-month regimen group and 82.6% in the 3-month regimen group. The adverse symptoms of fatigue/myalgia/weakness were experienced by six patients (31.6%) in the 2-month regimen group and six patients (26.1%) in the 3-month regimen group. Rash/itching symptoms were reported by 2 patients (10.5%) in the 2-month regimen group and 2 patients (8.7%) in the 3-month regimen group. Nausea/vomiting symptom was experienced by one patient (5.3%) in the 2-month regimen group and two patients in the 3-month regimen group. The symptom of loss of

Table 1: Comparison of demographic and clinical characteristics of latent tuberculosis patients receiving 2HRZ plus HUEXC030 and 3HP regimens

	2HRZ plus HUEXC030 (n=19)	3HP (n=23)	P
Age (years), mean±SD	51.58±5.14	53.17±3.896	0.8025
Male	5 (26.3)	9 (39.1)	0.5146
Body weight (kg), mean±SD	60.95±2.63	61.52±2.63	0.8794
HCVD	4 (21.1)	4 (17.4)	0.9999
DM	3 (15.8)	5 (21.7)	0.7092
ESRD	0	3 (13.0)	0.2387
HBV	0	0	-
HCV	0	0	-

HRZ=Isoniazid + rifampin + pyrazinamide; HP=Isoniazid + rifapentine; HCVD=Hypertensive cardiovascular disease; DM=Diabetes mellitus; ESRD=End-stage renal disease; HBV=Hepatitis B virus; HCV=Hepatitis C virus; SD=Standard deviation

Table 2: Comparison of side effects between patients with latent tuberculosis infection receiving 2HRZ plus HUEXC030 and 3HP regimens

	2HRZ plus HUEXC030 (n=19)	3HP (n=23)	P
Treatment completion	14 (73.7)	19 (82.6)	0.7075
Adverse event			
Fatigue/myalgia/weakness	6 (31.6)	6 (26.1)	0.7422
Headache	0	0	-
Nausea/vomiting	1 (5.3)	2 (8.7)	0.9999
Fever/chills	0	0	-
Rash/itching	2 (10.5)	2 (8.7)	0.9999
Loss of appetite	3 (15.8)	0	0.9577

HRZ=Isoniazid + rifampin + pyrazinamide; HP=Isoniazid + rifapentine

appetite was observed in three patients (7.1%) in the 2-month regimen group.

Laboratory values of patients with LTBI receiving 2HRZ plus HUEXC030 and 3HP regimens are shown in Table 3. The mean value of creatinine was lower among patients receiving the 2-month regimen compared to those receiving the 3-month regimen (0.80 ± 0.043 vs. 3.2 ± 0.085 mg/dl, $P = 0.0485$). The values of AST, ALT, and total bilirubin before treatment were similar in both groups (19.05 ± 1.66 vs. 24.42 ± 3.30 U/L, $P = 0.1547$; 19.00 ± 2.61 vs. 23.30 ± 5.21 U/L, $P = 0.4724$; and 0.64 ± 0.07 vs. 0.72 ± 0.15 mg/dl, $P = 0.6383$ for the 2-month regimen group vs. 3-month regimen group, respectively). The values of AST, ALT, and total bilirubin 4 weeks after treatment were similar in both groups (20.25 ± 3.591 vs. 23.63 ± 1.972 U/L, $P = 0.3881$; 14.80 ± 3.056 vs. 20.63 ± 3.676 U/L, $P = 0.4080$; and 0.54 ± 0.07 vs. 0.63 ± 0.07 mg/dl, $P = 0.3985$, for the 2-month regimen group vs. 3-month regimen group, respectively). Two patients and one patient developed hepatotoxicity in the 2-month regimen and 3-month regimen groups, respectively (10.5% vs. 4.3%).

DISCUSSION

The present study demonstrates that LTBI patients receiving the 2-month regimen with HRZ plus HUEXC030 experience similar side effects, including hepatitis, as patients on the

3-month regimen with isoniazid and rifampentine. The treatment completion rate was similar in both treatment groups. This new combination treatment regimen may be an alternative in the treatment of LTBI.

Treatment of LTBI is an essential component of the TB elimination strategy.¹⁴ The traditional regimen comprises a 9-month-long treatment with isoniazid.¹⁵ Hepatotoxicity and decreased compliance are major concerns with the daily use of isoniazid for 9 months. Hasely *et al.* found that a 2-month regimen of daily rifampin and pyrazinamide is effective and resulted in similar hepatotoxicity levels compared to the 9-month regimen of isoniazid among HIV patients.^{16,17} The US CDC previously adopted the short pyrazinamide/rifampin regimen as an alternative therapy but no longer recommends it on account of severe hepatotoxicity.^{18,19} Sterling *et al.* found that another short-course 3-month regimen with isoniazid plus rifampentine had equivalent efficacy as the 9-month regimen with isoniazid and was an acceptable regimen on account of equivalent prophylaxis, similar side effects, and short-course treatment.

The 2-month regimen with isoniazid, rifampin, and pyrazinamide has been widely used in Portugal. This regimen had good intracellular activity, but the risk of hepatitis is still a concern. If overcome side effects of liver toxicity with isoniazid, rifampin and pyrazinamide, the two-month preventive administration can not only shorten treatment period but also improve safety treatment of LTBI. The side effect of hepatitis due to HRZ treatment is attributed to the accumulation of toxic metabolites of isoniazid, rifampin, and pyrazinamide in the liver. CYP2E1 and amidase play important roles in the metabolic pathways of isoniazid and pyrazinamide. HUEXC030 is both an inhibitor of CYP2E1 and amidase and was able to alleviate hepatitis in animal and human studies. The incidence of hepatotoxicity in this regimen group was also similar to the 3-month regimen group, implying that HUEXC030 may play a protective role against hepatitis during treatment with isoniazid and pyrazinamide.

The completion rate with the daily use of isoniazid for 9 months is 50%–80%.²⁰ Sterling *et al.* found about a 90% completion rate for the 3-month regimen. Evidence of the efficacy of interventions aimed at improving treatment adherence and completion showed that shorter treatment duration was significantly associated with increased adherence.²¹ We propose a 2-month regimen with isoniazid, rifampin, and pyrazinamide plus HUEXC030, with a shorter treatment duration than the 3-month regimen, thereby improving treatment adherence and completion rate.

The incidence of hepatotoxicity during various treatments of LTBI is around 1%–5%.^{5,6,8} The incidence of hepatotoxicity in our study was 10.5% and 4.3% in the 2- and 3-month

Table 3: Comparison of laboratory values of patients with latent tuberculosis infection receiving 2HRZ plus HUEXC030 and 3HP regimens

	2HRZ plus HUEXC030 (n=19)	3HP (n=23)	P
WBC, cells/mm ³	7326±517.1	7075±653.0	0.7720
Hemoglobin, g/dL	13.08±0.41	12.41±0.62	0.3580
Platelet, ×10 ³ cells/mm ³	270.789±15.260	252.300±32.074	0.5584
BUN, mg/dL	12.84±0.73	15.82±2.05	0.1127
Creatinine, mg/dL	0.80±0.043	3.2±0.085	0.0485
1 st AST, U/L	19.05±1.66	24.42±3.30	0.1547
1 st ALT, U/L	19.00±2.61	23.30±5.21	0.4724
1 st total bilirubin, mg/dL	0.64±0.07	0.72±0.15	0.6383
2 nd AST, U/L	20.25±3.591	23.63±1.972	0.3881
2 nd ALT, U/L	14.80±3.056	20.63±3.676	0.4080
2 nd total bilirubin, mg/dL	0.54±0.07	0.63±0.07	0.3985
Hepatotoxicity*	2 (10.5)	1 (4.3)	0.5813

*All values except the incidence rate of hepatotoxicity are presented mean±SD. WBC=White blood cell count; AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; BUN=Blood urea nitrogen; SD=Standard deviation; HRZ=Isoniazid + rifampin + pyrazinamide; HP=Isoniazid + rifampentine

regimens, respectively. The possible explanations for the higher incidence of hepatotoxicity in the 2-month regimen group are as follows. First, the sample size was small and may have influenced the results during the observation period. Second, although HUEXC030 in the 2-month regimen with isoniazid, rifampin, and pyrazinamide could alleviate hepatitis caused by isoniazid and pyrazinamide, rifampin-associated hepatotoxicity could not be prevented by HUEXC030.

There are several limitations in our study. First, our study is a pilot study and the sample size in each group was small. Further randomized controlled clinical trials are warranted to compare these two LTBI treatment regimens. Second, the study observation period was short; thus, the treatment efficacy could not be addressed in our study. Third, the excipient HUEXC030 is not available in every hospital, and the combination with isoniazid, rifampin, and pyrazinamide is not recommended in the current national treatment guidelines for LTBI, resulting in difficulty in extrapolation of our study results.

CONCLUSIONS

Our preliminary study showed that combination of isoniazid, rifampin, and pyrazinamide plus HUEXC030 was an acceptable regimen for treatment of LTBI. The course of treatment is shorter than other three major treatment regimens of LTBI. Further randomized controlled trials are recommended to extrapolate our study findings.

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Conflicts of interest

There are no conflicts of interest.

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