Tuberculosis 111 (2018) 121–126

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: www.elsevier.com/locate/tube

Drug Discovery and Resistance

Twelve-dose weekly rifapentine plus isoniazid for latent tuberculosis infection: A multicentre randomised controlled trial in Taiwan

Hsin-Yun Sun[a], Yi-Wen Huang[b,c], Wei-Chang Huang[d,e,f], Lih-Yu Chang[g], Pei-Chun Chan[h], Yu-Chung Chuang[a], Sheng-Yuan Ruan[a], Jann-Yuan Wang[a,*], Jann-Tay Wang[a]

[a] Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
[b] Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[c] Pulmonary and Critical Care Unit, Changhua Hospital, Department of Health, Changhua, Taiwan
[d] Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, 407, Taiwan
[e] Department of Medical Technology, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, 407, Taiwan
[f] Department of Life Sciences, National Chung Hsing University, Taichung, 407, Taiwan
[g] Department of Internal Medicine, National Taiwan University Hospital Hsinchu Branch, Hsinchu, Taiwan
[h] Department of Pediatrics, National Taiwan University Hospital and Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taiwan

ARTICLE INFO

Keywords:
Hepatotoxicity
Isoniazid
Latent tuberculosis infection
Preventive therapy
Rifapentine

ABSTRACT

Treatment of latent tuberculosis (TB) infection (LTBI) effectively prevents its progression to active TB. However, long treatment duration and drug-related hepatotoxicity limit the effectiveness of the 9-month daily isoniazid (9H). Data on the 3-month weekly rifapentine plus isoniazid (3 HP) in Asian populations are currently unavailable. We prospectively randomised the LTBI contacts aged ≥ 12 years with positive tuberculin skin test into 9H and 3 HP groups in four hospitals between January 2014 and May 2016 in Taiwan. The primary and secondary outcomes were treatment completion rate and adverse drug reactions (ADRs), respectively. Overall, 263 participants with LTBI were randomised into the 3 HP (n = 132) and 9H groups (n = 131); 14 (10.6%) and 29 (22.1%) participants in the 3 HP and 9H groups, respectively, discontinued therapy (p = 0.011). Discontinuation rates owing to ADRs were 9.1% (3 HP) and 5.3% (9H) (p = 0.241). Clinically relevant hepatotoxicity was more common in the 9H than in the 3 HP group (5.3% vs. 1.5%; p = 0.103), whereas systemic drug reaction was more common in the 3 HP than in the 9H group (3.8% vs. 0%; p = 0.060). Women had a significantly higher rate of Grade II fever than men (13.7% vs. 1.2%; p = 0.003). Compared with the 9H regimen, the 3 HP regimen had a higher completion rate with lower hepatotoxicity and well-tolerated ADR.
Clinical trials registration: number NCT02208427.

1. Introduction

Tuberculosis (TB) remains one of the most deadly communicable diseases [1]. The ambitious targets of the End TB Strategy of the World Health Organization (WHO) are 95% reduction in TB-related deaths and 90% reduction in the incidence rate of TB by 2035 [2]. This implies intensified case finding and the introduction of preventive therapy for individuals with latent TB infection (LTBI) [1], carrying an approximately 10% lifetime risk of progression to active TB [3].

Studies demonstrated that treatment with isoniazid reduced the risk by approximately 60% in HIV-negative individuals at a high risk of active TB for more than 2 years [4]. However, among the patients receiving the 9-month isoniazid treatment, isoniazid-associated hepatotoxicity was observed in 2.7%, Grade 3 or 4 hepatotoxicity in 0.3% and isoniazid treatment discontinuation in 2% [5]. Shortened rifampicin monotherapy and rifampicin-combination therapy have been designed to reduce the treatment duration, exposure to hepatotoxic isoniazid and to increase completion rate [5–7]. The 3-month regimen of weekly rifapentine plus isoniazid (3 HP regimen) has been shown to exhibit higher completion rates (82.1% vs. 69.0%, p < 0.001) and lower liver toxicity (0.4% vs. 2.7%, p < 0.001) than the 9-month regimen of daily isoniazid (9H regimen) [5]. However, higher rates of treatment discontinuation owing to adverse drug reactions (ADRs) were observed in the 3 HP group than in the 9H group (4.9% vs. 3.7%, p = 0.009) in a prospective, open-label, randomised trial (the PREVENT TB study) [5].

* Corresponding author.
E-mail addresses: jywang@ntu.edu.tw, 008758@ntuh.gov.tw (J.-Y. Wang).

https://doi.org/10.1016/j.tube.2018.05.013
Received 18 March 2018; Received in revised form 6 May 2018; Accepted 20 May 2018

The incidence of TB in Taiwan has declined from 72.5 per 100,000 population in 2005 to 53 in 2012 after an intensified effort to control TB in Taiwan using the implementation of a directly observed therapy (DOT) short-course programme for all patients with TB since 2006 along with more laboratory diagnosis, contact investigation, and LTBI treatment [8]. The completion rate of TB contact investigation is more than 95%, and the 9H regimen was the mainstay treatment option until April 1, 2016, when the 3 HP regimen began to be implemented [9]. Nevertheless, data regarding the 3 HP regimen in Asian populations are relatively scanty. Thus, in this prospective randomised study, we compared the treatment completion rates and incidence rates of ADRs among individuals with LTBI undergoing the 9H and 3 HP regimens in Taiwan.

2. Methods

2.1. Study design

This was a prospective, open-label, multicentre randomised trial involving close contacts of index patients with a new diagnosis of pulmonary TB with positive acid-fast bacilli (AFB) between January 2014 and May 2016. The study was approved and conducted in four hospitals, the Taipei and Hsin-Chu branches of National Taiwan University Hospital (NTUH), Taichung Veterans General Hospital, and the Ministry of Health and Welfare Hospital in Changhua (NTUH, 201309055MINC; NTUH Hsinchu Branch 103-079-F; TVGH SF14273B). The enrolled close contacts were randomly allocated (1:1) to the 3 HP and 9H group (see study protocol for details).

2.2. Study population

Participants were eligible for enrolment if they were aged ≥12 years and close contacts of AFB-positive pulmonary TB patients and positive tuberculin skin test (TST) within 1 month after unprotected exposure. A positive TST was defined as an induration of ≥10 mm read at 48–72 h after inoculation and an unprotected exposure as exposure duration of ≥8 h in a single day or a cumulative duration of ≥40 h without adequate personal protective equipments for preventing airborne disease transmission.

This study excluded the participants if their index patients had negative sputum cultures for *Mycobacterium tuberculosis* complex, though smear-positive for AFB, or *M. tuberculosis* complex with resistance to isoniazid or rifampin and those who were suspected to have active pulmonary TB because of clinical symptoms or image examinations, concurrently using drugs with severe drug–drug interactions with or allergic to isoniazid, rifampin, or rifapentine (see study protocol for details).

2.3. Randomisation and follow-up

After written informed consent was obtained, every participant underwent chest radiography, hepatitis B surface antigen (HBsAg), anti–hepatitis C virus antibody (anti-HCV), anti–human immunodeficiency virus antibody (anti-HIV), renal and liver function tests, and the QuantiFERON-TB Gold In-Tube (QFT) test at screening.

A random allocation sequence was generated using a computer software programme in NTUH by the principal investigator (see study protocol for details). The participants were assessed on day 1 (baseline) and at weeks 4, 8, and 12 in the 3 HP group and every 4 weeks until week 36 in the 9H group. All the participants were followed up until early termination, the development of active TB, or 2 years after treatment completion. If respiratory symptoms existed, at least two sputum specimens were sent for AFB and mycobacterial culture.

During the treatment, blood tests to monitor full blood count, liver and renal function tests were conducted every month for 3 months and every 2 months thereafter if indicated for the 9H group. DOT was implemented by the research assistants and government-paid supporters to assess the adherence of the participants. The research assistants contacted all participants every week in person or by telephone to inquire about any ADRs after the treatment.

Chest radiography and QFT were conducted for all participants 1 and 2 years after treatment completion. If TB-like symptoms developed during follow-up, relevant investigations were initiated to confirm the diagnosis of active TB, defined as the isolation of *M. tuberculosis* complex from the clinical specimens, demonstration of granulomatous inflammation in clinical specimens or consistent radiographic findings and clinical symptoms plus a favourable response to antituberculous therapy.

2.4. Outcomes

The primary endpoint was treatment completion; defined as the completion of the 270-day treatment within 12 months in the 9H group and completion of the 12-dose treatment within 3 months in the 3 HP group. The completion rates were analysed in the intention-to-treat populations. Reasons for early discontinuation of preventive therapy were determined. The secondary endpoint was incidence of severe ADRs in each study group.

2.5. ADRs

Hepatotoxicity was defined as a 2-fold or greater increase in the AST/ALT or total bilirubin level from the baseline [10], whereas clinically relevant hepatotoxicity was defined as a 5-fold or greater increase in the AST/ALT level, 3-fold or greater increase with clinical symptoms, or total bilirubin level > 3 mg/dL [11]. The probability of ADRs of the study drugs was determined using the Naranjo algorithm [12]. A Naranjo score of 5–8 indicates probable ADRs, and a score > 9 indicates definite ADRs [12]. The grading of ADR was also determined by Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events [13]. Systemic drug reaction (SDR) was defined as previously reported [14].

2.6. Statistical analysis

The sample size was calculated based on two reports [5,15]. The completion rate was 59.7% (255/427) for 9H in one [15], and the completion rate was 69.0% and 82.1% for 9H and 3 HP, respectively, in another [5]. Totally, the completion rate of 9H was 68.1%. To have a power of 0.8 and an alpha error of 0.95 in a two-sided test for the difference in completion rate, the calculated sample size is 148 for each arm. Considering late exclusion due to INH and RMP resistance (9% and 2%, respectively) and the possibility of index cases having culture-negative pulmonary TB, the sample size becomes 161 for each arm. However, significant differences between the two groups were noted in the mid-term analysis. Thus, the study stopped enrolled new cases before the targeted numbers were reached.

Collected data included age, sex, height, weight, systemic diseases, medication, laboratory test and image results, study drugs, ADRs, and medical records of the participants. To evaluate the between-group differences, categorical variables were compared using χ^2 or the Fisher exact test whereas continuous variables were compared using the Student *t*-test or Mann–Whitney *U* test. Only variables with two-tailed *p* values of less than 0.05 were considered statistically significant.

3. Results

During the study period, 339 TST-positive close contacts of AFB-positive TB patients were screened for eligibility; however, 41 refused to participate and 15 had screen failure. Thus, 283 participants were eligible for enrolment; 142 were randomised to the 3 HP group and 141 to the 9H group. After the late exclusion of ten participants from each