



Adverse event and treatment completion rates of a 12-dose weekly isoniazid and rifapentine course for South Korean healthcare workers

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ABSTRACT

Purpose: We investigated the adverse events (AEs) and treatment completion rates of a 3 month course of once-weekly isoniazid and rifapentine (3H₁P₁) in South Korean health care workers (HCWs) with latent tuberculosis infection (LTBI).

Methods: HCWs who were candidates for LTBI treatment were enrolled from two tertiary referral centers between December 2016 and October 2017. From December 2016 through March 2017, HCWs who agreed were treated with the 3H₁P₁ regimen (3H₁P₁ group). Their compliance and AEs were prospectively collected. From April 2017 onward, HCWs who required LTBI treatment received 3 months of isoniazid plus rifampin (3HR group), and their medical records were retrospectively reviewed.

Results: During the study period, 406 HCWs were treated, 226 (55.7%) in the 3H₁P₁ group, and 180 (44.3%) in the 3HR group. The number of subjects with AEs was significantly greater in the 3H₁P₁ group (75.2% vs 56.7%, $P < 0.001$), in particular a flu-like syndrome (19.0% vs. 0%, $P < 0.001$). However, hepatotoxicity occurred less frequently in those receiving 3H₁P₁ (7.5% vs. 20.0%, $P < 0.001$). Per protocol definition, anaphylaxis developed in 1.8% of the 3H₁P₁ group. The overall treatment completion rate was greater in the 3H₁P₁ group (92.9% vs 86.7%, $P = 0.036$).

Conclusions: The 3H₁P₁ regimen had a higher treatment completion rate and lower hepatotoxicity compared with the 3HR regimen. However, it resulted in a higher rate of flu-like syndromes. Additionally, a few subjects had anaphylaxis, although there were no fatalities.

1. Introduction

Several options are available for the treatment of latent tuberculosis infection (LTBI): 6-months or 9-months of isoniazid (6H or 9H), 3 months of once-weekly isoniazid and rifapentine (3H₁P₁), 3 months of isoniazid plus rifampin (3HR) or 4 months of rifampin alone. Among these regimens, the most recent, and perhaps most promising short-course regimen, is 3H₁P₁. The Centers for Disease Control and Prevention (CDC) recommended the use of 3H₁P₁ for persons 12 years or older [1], based on the results of an open-label, randomised trial of 3H₁P₁ vs

9H [2]. Recently published World Health Organization (WHO) guidelines stated that 3H₁P₁ may be offered as an alternative to 6H as treatment for LTBI in countries with a high and low tuberculosis (TB) incidence [3], on the basis of their systematic review covering four randomised controlled trials [2,4–6]. Since a shorter duration leads to better protocol adherence, less hepatotoxicity, more cost-effectiveness and a higher treatment completion rate, 3H₁P₁ regimen is increasingly preferred [7–9]. However, a significant number of patients treated with 3H₁P₁ had systematic drug reactions (SDR), in particular flu-like symptoms [10]. Additionally, 3H₁P₁ may rarely cause serious adverse

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events such as hypotension, which require permanent drug discontinuation [2,10]. In a randomised trial of 3H₁P₁ vs 9H published in 2011 [2], permanent discontinuation of the regimen because of serious adverse drug events was more frequent with 3H₁P₁ than 9H (4.9% vs. 3.7%, $P = 0.009$). In a recently published randomised controlled trial in China, treatment with the 3H₁P₁ regimen had to be modified early on due to the unexpected high frequency of adverse event [11].

The incidence of TB in South Korea remains the highest among high-income countries. TB incidence in South Korea was seven times greater than the average incidence for member countries of the Organization for Economic Co-operation and Development [12]. To reduce this burden, active diagnosis as well as better treatment of LTBI is increasingly emphasised in South Korea [13]. Despite the high prevalence of LTBI, particularly among the elderly in South Korea [14,15], the rifampine containing regimen is currently not available. One reason is the lack of data concerning tolerability or adverse drug reactions among the South Korean LTBI patients. In order for a rifampine containing regimen to be used, such data should first be obtained. Therefore, the present study was conducted to investigate the rate of treatment completion and adverse drug events of the 3H₁P₁ regimen in South Korean health care workers (HCWs) with LTBI, in order to assess whether this regimen can be safely used for LTBI treatment in South Korea.

2. Materials and methods

2.1. Study subjects

This study was planned with the Korean CDC (KCDC). To determine whether 3H₁P₁ regimens could be used in the general population with LTBI, we first determined the tolerability of this regimen in HCWs who required LTBI treatment. HCWs were enrolled from two tertiary referral centers (Asan Medical Center in Seoul and Incheon St. Mary's Hospital in Incheon) in South Korea between December 2016 and October 2017. During this period, as a part of a national TB elimination programme, almost all HCWs in the two centers underwent a QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis/Qiagen, Carnegie, Australia). Among HCWs with a positive QFT-GIT assay, those who were identified as candidates for LTBI treatment by their attending physician were screened for the present study. The decision to treat was based on South Korean guidelines [16]. In brief, a HCW was considered to be a candidate for LTBI treatment if (i) he or she had no previous history of adequate treatment for TB or LTBI and (ii) the possibility of active TB had been completely excluded. All the candidates were encouraged to receive LTBI treatment. This study was approved by the Institutional Review Board of each center.

2.2. Treatment with 3H₁P₁ – the study group

Those HCWs whose treatment decision was made between December 2016 and March 2017 were screened for the 3H₁P₁ study. All HCWs provided written informed consent concerning 3H₁P₁ treatment before enrollment. After instruction regarding the regimen and its potential adverse events, only those who agreed to receive the 3H₁P₁ regimen for their LTBI treatment were enrolled and treated with 3H₁P₁ (3H₁P₁ group). Those refusing 3H₁P₁ were offered 9H or 3HR. The medical records of HCWs receiving 3H₁P₁ were prospectively collected by their attending physician and public-private-mix (PPM) nurses at each center. Rifampine was acquired through the KCDC and supplied free of charge. It was administered at a dose of 900 mg for subjects weighing >50 kg and 750 mg for those weighing ≤50 kg. Isoniazid was administered at a dose of 15 mg/kg body weight rounded up to the nearest 50 mg or 100 mg, with a maximum dose of 900 mg. Each dose of 3H₁P₁ was administered weekly under directly observed therapy (DOT) by PPM nurses in each center to monitor for adverse events and encourage adherence for each weekly visit. PPM nurses recorded adverse event and compliance data into an electronic database. HCWs who did not tolerate

the 3H₁P₁ regimen because of serious adverse events were switched to 9H or 3HR, or had their treatment discontinued entirely according to the attending physician's discretion. Laboratory tests were performed at the baseline visit and 4 and 12 weeks after treatment initiation. For HCWs who had liver disease such as fatty liver, liver function tests were obtained more frequently.

2.3. Treatment with 3HR – the control group

After April 2017, HCWs requiring LTBI treatment were managed according to each center's routine protocol. During this period, the 3HR regimen was primarily selected for LTBI treatment at both centers, because a previous study in South Korea showed that this regimen had the highest completion rate [17]. Medical records of HCWs receiving the 3HR regimen (3HR group) between April 2017 and October 2017 were retrospectively reviewed and compared with those of the 3H₁P₁ group. Follow-up visits and laboratory tests were performed according to the routine protocol of each center, usually at 4 and 12 weeks after treatment initiation.

2.4. Adverse events analysis

All adverse events were measured and graded by each investigator using common terminology criteria for adverse events (CTCAE) version 4.0 [18]. Flu-like syndromes were defined as a group of symptoms similar to those observed in patients with the flu, including fever, chills, body aches, malaise, loss of appetite and dry cough. Anaphylaxis were defined as the presence of any of the following complications associated with medication for LTBI treatment; (i) symptomatic bronchospasm, with or without urticaria; (ii) parenteral intervention indicated; (iii) allergy-related oedema/angioedema and (iv) hypotension [18].

2.5. Interim assessments

After initiating treatment with the 3H₁P₁ regimen, several HCWs unexpectedly had anaphylaxis. The study investigators urgently convened a data and safety monitoring board (DSMB), although the original study protocol did not include it. The DSMB comprised several TB experts and representatives of the KCDC and the Ministry of Food and Drug Safety. Given the episodes of anaphylaxis among several subjects, the DSMB and study investigators discussed whether treatment with the 3H₁P₁ regimen should be continued. The DSMB recommended discontinuing recruitment of subjects for 3H₁P₁ treatment, based on the unexpected reports of anaphylaxis episodes. However, for the subjects who had already initiated and were tolerating the 3H₁P₁ regimen, the DSMB recommended continuing the treatment along with careful observation. The study investigators accepted this recommendation. No further episodes of anaphylaxis in the 3H₁P₁ group were reported.

2.6. Statistical analysis

All data are presented as means ($\pm$ standard deviations) for continuous variables, and percentage for categorical variables. Data were compared by Student's *t*-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. All tests were two-sided and *P* values less than 0.05 were considered statistically significant. All data were analysed using SPSS software (version 24.0; SPSS, Chicago, IL).

3. Results

3.1. Characteristics of the study subjects

Between December 2016 and March 2017, 307 HCWs were screened for the 3H₁P₁ study, of whom, 226 (73.6%) agreed to receive the 3H₁P₁ regimen and were enrolled. In addition, between April 2017 and October 2017, 234 HCWs were recommended to undergo treatment for

LTBI, of whom, 180 (76.9%) accepted the attending physician's recommendation and received LTBI treatment with 3HR regimen (Fig. 1). Therefore, between December 2016 and October 2017, 406 HCWs received treatment; 226 (55.7%) in the 3H₁P₁ group between December 2016 and March 2017, and the remaining 180 (44.3%) in the 3HR group between April 2017 and October 2017 (Fig. 1). The subjects' mean age was 43.1 ± 11.7 years, and 66.7% were female. The baseline characteristics of the two groups are noted in Table 1.

3.2. Adverse events rates between the two groups

Among the 406 HCWs who received 3H₁P₁ or 3HR, 272 (67.0%) had one or more adverse events associated with LTBI treatment regimen. The percentage of subjects with any adverse event was significantly higher in the 3H₁P₁ group (75.2% vs 56.7%, $P < 0.001$, Table 2). As noted in Table 2, there was no significant between-group difference in the percentage of participants with a grade 3 or 4 adverse event. However, the percentage of subjects with any grade 1 or 2 adverse event was higher in the 3H₁P₁ group (71.7% vs 55.6%, $P = 0.001$, Table 2).

Table 3 presents the detailed adverse events of the study subjects. Hepatotoxicity with a grade 1 or 2 adverse event occurred less frequently among those receiving 3H₁P₁ (7.5% vs. 20.0%, $P < 0.001$). However, the percentage of subjects with headache, flu-like syndrome and dizziness was significantly higher in the 3H₁P₁ group. The median cumulative dose from treatment initiation to onset of adverse events was 3 weeks in the 3H₁P₁ group. Most (89.6%) adverse events occurred

Table 1

Clinical characteristics of 406 healthcare workers based on treatment regimen.

Characteristics	Total subjects (n = 406)	3H ₁ P ₁ group (n = 226)	3HR group (n = 180)	P value
Age, years	43.1 ± 11.7	42.9 ± 10.7	43.5 ± 12.9	0.637
Female gender	271 (66.7)	143 (63.3)	128 (71.1)	0.096
Hospitals where HCWs were enrolled				0.009
Asan Medical Center	203 (50.0)	100 (44.2)	103 (57.2)	
Incheon St. Mary's Hospital	203 (50.0)	126 (56.5)	77 (42.8)	
Chronic liver disease				
Fatty liver	14 (3.4)	11 (4.9)	3 (1.7)	0.025
Chronic hepatitis B	3 (0.7)	3 (1.3)	0	0.258
Hepatitis B virus carrier	4 (1.0)	1 (0.4)	3 (1.7)	0.326

3H₁P₁, 3 months of once-weekly isoniazid and rifapentine; 3HR, 3months isoniazid plus rifampin.

Data are reported as mean ($\pm$ standard deviation) and numbers (%).

within the administration of 5 doses after treatment initiation (Fig. 2).

3.3. Development of anaphylaxis

Anaphylaxis developed in 4 (1.8%) of the 226 subjects receiving the

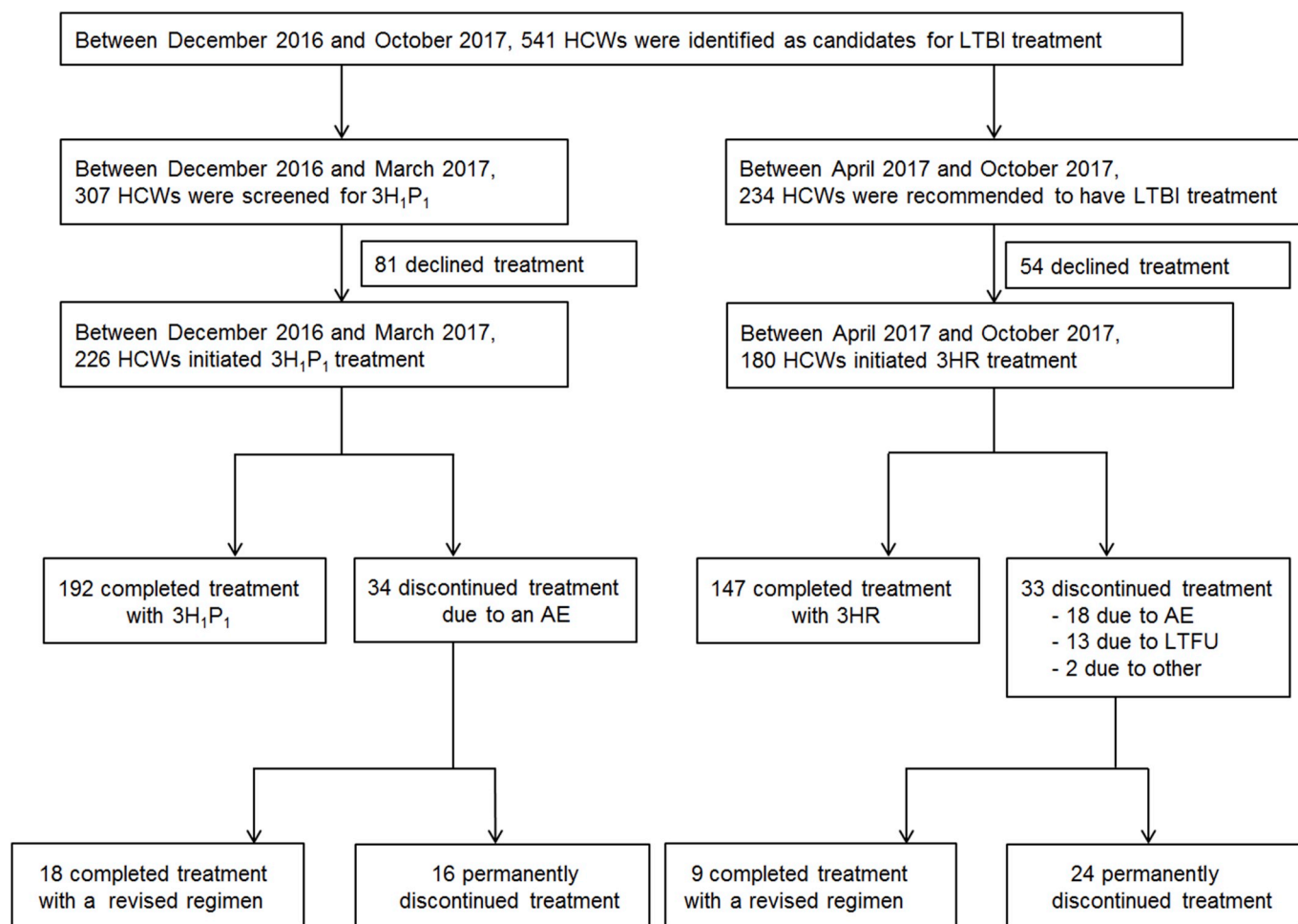


Fig. 1. Study flow chart.

HCW, healthcare worker; 3H₁P₁, 3 months of once-weekly isoniazid and rifapentine; 3HR, 3months isoniazid plus rifampin; AE, adverse events, LTFU, lost to follow-up.

Table 2

Adverse events and treatment completion rates of subjects by treatment regimen.

	Total subjects (n = 406)	3H ₁ P ₁ group (n = 226)	3HR group (n = 180)	P value
Adverse events				
No. of subjects with any adverse events	272 (67.0)	170 (75.2)	102 (56.7)	<0.001
No. of subjects with any grade 3 or 4 adverse events	10 (2.5)	8 (3.5)	2 (1.1)	0.074
No. of subjects with any grade 1 or 2 adverse events	262 (64.5)	162 (71.7)	100 (55.6)	0.001
Treatment completion				
No. of total subjects with treatment completion	366 (90.1)	210 (92.9)	156 (86.7)	0.036
No. of subjects with treatment completion with original regimen	339 (83.5)	192 (85.0)	147 (81.7)	0.375
No. of subjects discontinued treatment of original regimen	67 (16.5)	34 (15.0)	33 (18.3)	0.375
Drug adverse events	52 (12.8)	34 (15.0)	18 (10.0)	0.131
Lost to follow up	13 (3.2)	0	13 (7.2)	<0.001
Others	2 (0.5)	0	2 (1.1)	0.196

3H₁P₁, 3 months of once-weekly isoniazid and rifapentine; 3HR, 3months isoniazid plus rifampin.

Data are reported as numbers (%).

Table 3

Detailed adverse events of study subjects according to the grade and symptoms.

	Total subjects (n = 406)	3H ₁ P ₁ group (n = 226)	3HR group (n = 180)	P value
Grade 3 or 4 adverse events*				
Anaphylaxis	4 (1.0)	4 (1.8)	0	0.133
Hepatotoxicity	3 (0.7)	2 (0.9)	1 (0.6)	>0.99
Urticaria	2 (0.5)	1 (0.4)	1 (0.6)	>0.99
Dizziness	1 (0.2)	1 (0.4)	0	>0.99
Grade 1 or 2 adverse events*				
Fatigue	80 (19.7)	51 (22.6)	29 (16.1)	0.104
Hepatotoxicity	53 (13.1)	17 (7.5)	36 (20.0)	<0.001
Urticaria	51 (12.3)	34 (15.0)	17 (9.4)	0.091
Headache	50 (12.3)	45 (19.9)	5 (2.7)	<0.001
Nausea	48 (11.8)	32 (14.2)	16 (8.9)	0.102
Flu-like syndromes	43 (10.6)	43 (19.0)	0	<0.001
Abdominal pain	40 (9.9)	21 (9.3)	19 (10.6)	0.671
Dizziness	38 (9.4)	30 (13.3)	8 (4.4)	0.002
Leukopenia	24 (5.9)	10 (4.4)	14 (7.8)	0.155
Papular rash	22 (5.4)	12 (5.3)	10 (5.6)	0.913
Fever with or without chills	18 (4.4)	10 (4.4)	8 (4.4)	0.992
Diarrhoea	11 (2.7)	9 (4.0)	2 (1.1)	0.122
Peripheral dysesthesia	10 (2.5)	5 (2.2)	5 (2.7)	0.756
Thrombocytopenia	3 (0.7)	0	3 (1.7)	0.086
Others	26 (6.4)	22 (9.9)	2 (1.1)	<0.001

*Subjects could have more than one type of serious adverse event.

3H₁P₁, 3 months of once-weekly isoniazid and rifapentine; 3HR, 3months isoniazid plus rifampin.

Data are reported as numbers (%).

3H₁P₁ regimen, while none of the 3HR group had anaphylaxis. The median time for the occurrence of anaphylaxis was after the sixth weekly dose, and the median time from drug ingestion to symptom onset was 75 min. The detailed clinical manifestations of anaphylaxis are summarised in Table 4. One subject required subcutaneous epinephrine to relieve her symptoms. This subject received a skin test to confirm the

diagnosis of anaphylaxis. The result was positive at a dilution of 0.02 mg/mL of rifapentine, which confirmed an IgE-mediated hypersensitivity reaction (Online supplementary data).

3.4. Treatment completion rate

Of the 406 subjects, 366 (90.1%) completed LTBI treatment. The overall treatment completion rate was higher in subjects receiving the 3H₁P₁ regimen (92.9% vs 86.7%, $P = 0.036$, Table 2). Most (83.5%, 339/406) subjects completed treatment without changing regimens; the treatment completion rate with the original regimen was similar between the two groups (Table 2). The primary reason for treatment discontinuation in both groups was adverse effects of the drugs. The second most common reason for treatment discontinuation in the 3HR group was being lost to follow-up.

4. Discussion

In the present study, we aimed to assess the tolerability of the 3H₁P₁ regimen for LTBI patients in South Korea by prospectively collecting information on adverse events and treatment completion rate for 226 HCWs. The most important finding of the present study was that subjects receiving 3H₁P₁ had (i) more grade 1 or 2 adverse events, particularly flu-like syndrome, (ii) less hepatotoxicity and (iii) generally higher treatment completion rates, compared to those treated with the 3HR regimen. However, most importantly, 1.8% (4/226) of HCWs had anaphylaxis after 3H₁P₁ treatment.

The PREVENT study, which became a landmark of the 3H₁P₁ regimen, was conducted as an open-label randomised non-inferiority trial which compared directly observed 3H₁P₁ with self-administered 9H [2]. This study found that 3H₁P₁ was as effective as 9H in preventing TB (cumulative rate of TB was 0.19% vs 0.43%), and had a higher treatment completion rate (82.1% vs 69.0%). This trial was the basis for the CDC guidelines in 2011, which stated that 3H₁P₁ by DOT is recommended as an equal alternative to 9H for treating LTBI [1]. Subsequent study reported that the risk for hepatotoxicity of 3H₁P₁ was significantly lower [19]. Additionally, a higher treatment completion rate with 3H₁P₁ was also noted in the setting of clinic-based DOT [20]. Recently, Belknap and colleagues found that self-administered 3H₁P₁ treatment could be used in some settings [21], by demonstrating similar completion rates for directly observed versus self-administered treatment with 3H₁P₁ in an open-label phase IV randomised non-inferiority clinical trial [22]. One study showed that 3H₁P₁ may be a cost-effective alternative to 9H [9]. Based upon all of these studies, WHO recently updated their recommendations to include 3H₁P₁ as a treatment option in countries with a high incidence of TB [23]. In our study, subjects treated with directly observed 3H₁P₁ also had a higher treatment completion rate and a lower risk of hepatotoxicity compared with a conventional self-administered 3HR regimen.

However, patients treated with 3H₁P₁ have clinically significant SDRs more frequently. Sterling et al. evaluated reactions with systemic manifestations in all participants in the PREVENT trial [10]. They found that SDR occurred significantly more frequently among patients who received 3H₁P₁ than 9H (3.5% vs 0.4%, $P < 0.001$), of which the most common presentation was a flu-like syndrome which accounted for 63% of the total SDR episodes with 3H₁P₁. This flu-like syndrome is known to be associated with rifampin antibodies [24]. Treatment with the 3H₁P₁ regimen could result in a flu-like syndrome more commonly than other regimens because the flu-like syndrome has been reported with intermittent and high doses of rifampin [25–27]. However, in the present study, a flu-like syndrome in the 3H₁P₁ group was relatively more common [19.0% (43/226) of our subjects] than that reported in the PREVENT trial. Although the underlying mechanism of this discrepancy between the findings of our study and those of the PREVENT trial is unclear, differences in race, sex, age, or body mass index (BMI) of the two study populations may be a plausible explanation.

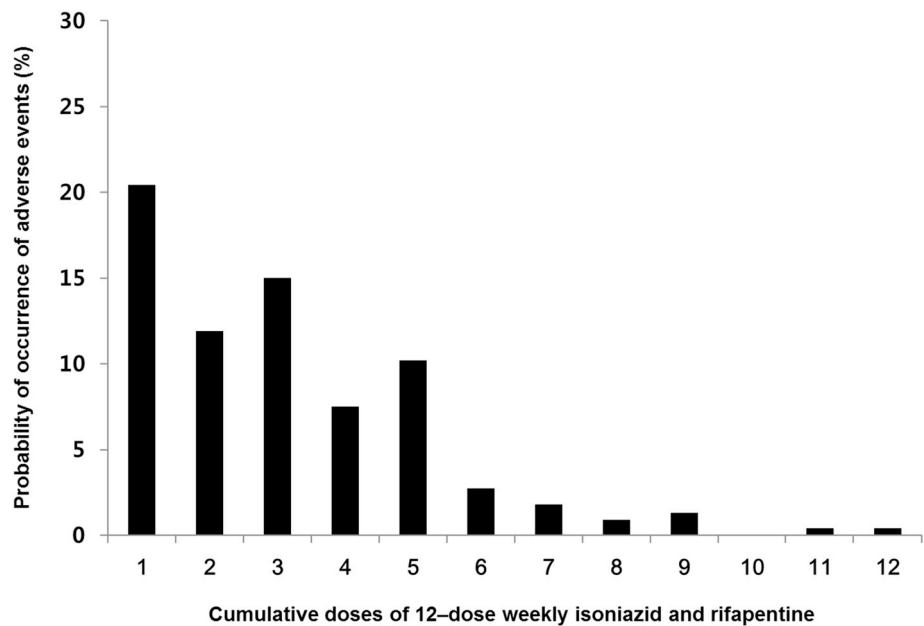


Fig. 2. Cumulative doses of 12-dose weekly isoniazid and rifapentine before the development of adverse events.

Table 4
Detailed characteristics of four subjects with anaphylaxis.

	Subject 1	Subject 2	Subject 3	Subject 4
Age, years	49	27	28	44
Gender	Female	Female	Female	Male
Weight, Kg	53	52	63	82
Body mass index, Kg/m ²	21.9	20.3	23.7	24.8
Doses received prior to event onset	4	5	6	8
Time from drug ingestion to event onset (minutes)	40	60	90	90
Manifestations				
Dermatologic	Generalised urticaria	Localised urticaria	Angioedema, localised urticaria	none
Cardiovascular	Hypotension	none	none	none
Respiratory	Symptomatic bronchospasm	Symptomatic bronchospasm	Upper airway swelling	Symptomatic bronchospasm
Intervention	Subcutaneous epinephrine	Oral anti-histamine	Intravenous steroid	Intravenous steroid
Skin test (IgE mediated)	Positive	Not performed	Not performed	Not performed

The most serious adverse event in the 3H₁P₁ group of the present study was anaphylaxis, which developed in 1.8%, although it was not life-threatening. Among subjects enrolled in the PREVENT trial, 3.8% (152/4040) had a possible hypersensitivity reaction [2]. Among them, six had a systolic blood pressure of less than 90 mmHg. However, after carefully reviewing and redefining the adverse events, Sterling et al. concluded that no case of anaphylaxis developed in the 3H₁P₁ group in the PREVENT trial [10]. Although 3.4% of patients in a recently published study in China treated with standard dose 3H₁P₁ regimen had hypersensitivity or an allergic reaction, it was not reported whether there were any cases of anaphylaxis among the patients with hypersensitivity [11]. To our knowledge, there have been no reports in the literature of the 3H₁P₁ regimen inducing anaphylaxis, while 1.8% of our subjects had anaphylaxis. This discrepancy may be explained by the differences in the definition of anaphylaxis. We defined anaphylaxis as the presence of any of the following: (i) symptomatic bronchospasm, with or without urticaria; (ii) parenteral intervention indicated; (iii) allergy-related oedema/angioedema; and (iv) hypotension [18]. In contrast, anaphylaxis was defined more strictly in the previous study; at least one major dermatological reaction as well as at least one cardiovascular and/or respiratory criterion [10], according to the case definition and guideline for anaphylaxis data collection [28]. However, if this more strict criterion were applied to our study, 0.9% (2/226,

subjects 1 and 2 in Table 4) would still be defined as having anaphylaxis, particularly subject 1 whose diagnosis was confirmed by an IgE-mediated skin test. Even though there were no mortalities from anaphylaxis in our study, we felt that 1.8% of subjects with anaphylaxis are significant, considering that all of our subjects were healthy. Based on this study, it would appear prudent not to prescribe the 3H₁P₁ regimen to the general population with LTBI in South Korea. However, since the 3H₁P₁ regimen also has the distinct advantage of a high treatment completion rate and low hepatotoxicity, a rifapentine containing regimen may be worth careful use in some patients. For instance, despite a high prevalence of LTBI in the elderly in South Korea, LTBI treatment is not recommended for the patients older than 65 years of age due to potential hepatotoxicity [16]. A rifapentine containing regimen could be considered for groups with a concern for hepatotoxicity. This suggestion was supported by a recent report which noted the feasibility of achieving a high completion rate for 3H₁P₁, even among the elderly [29]. Because adverse events including anaphylaxis mostly occur within the first 5 weeks of treatment, care should particularly be taken during this period following rifapentine prescription. A flu-like syndrome seemed to occur less frequently in patients initially treated with lower, daily dosing of rifamycin [30,31]. Additionally, those who develop flu-like syndrome on high-dose intermittent regimens often tolerate subsequent lower daily dosing [32]. Gao et al.

found that a 2-month twice-weekly regimen of rifapentine plus isoniazid, with a maximum dose of 600 mg for each, was quite effective with an acceptable safety profile [11]. Recently, Swindells et al. showed that a 1-month regimen of daily rifapentine (600 mg for weight >45 kg) plus isoniazid (300 mg) was noninferior to 9 months of isoniazid alone for preventing TB in HIV-infected patients [33]. Notably, no hypersensitivity reactions were reported in that study [33]. All of these studies suggest that a different dosing schedule, frequent administration (twice-weekly or daily) with a lower dose of rifapentin (maximum dose of 600 mg) and isoniazid (maximum dose of 300–600 mg), could possibly result in equivalent prevention with fewer serious adverse events including flu-like syndrome or anaphylaxis. Further study is needed to elucidate this issue.

Although our research had the advantage of being conducted for a homogenous population of HCWs, there were several limitations. First, the 3HR group received treatment in a self-administered manner and their adverse events were collected retrospectively, while the adverse events were prospectively collected under DOT in the 3H₁P₁ group. This difference might have led to the lower treatment completion rate and lower frequency of adverse events noted in the 3HR group. If the 3HR group had received DOT, it is possible that the treatment completion rate might have been higher. Also, some adverse events, especially the milder ones, were likely not reported in the 3HR group. Second, anaphylaxis was not confirmed in three of the four subjects by means of an IgE-mediated skin test.

In conclusion, South Korean HCWs with LTBI treated with the 3H₁P₁ regimen had a higher treatment completion rate and less hepatotoxicity when compared with those receiving the 3HR regimen. However, treatment with the 3H₁P₁ regimen resulted in a higher rate of SDR such as flu-like syndromes and a 1.8% rate of anaphylaxis. These findings suggest that the 3H₁P₁ regimen might not be appropriate for widespread use among the general population with LTBI in South Korea. However, since the rifapentine containing regimen has advantages in terms of short treatment duration and low hepatotoxicity, it could be used cautiously in selected population with LTBI, such as the elderly with a risk for hepatotoxicity. Further study with a different dosage or dosing schedule of rifapentine is worthwhile, as this modified regimen could possibly have a lower rate of adverse events.

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Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.10.005>.

References

- found that a 2-month twice-weekly regimen of rifapentine plus isoniazid, with a maximum dose of 600 mg for each, was quite effective with an acceptable safety profile [11]. Recently, Swindells et al. showed that a 1-month regimen of daily rifapentine (600 mg for weight >45 kg) plus isoniazid (300 mg) was noninferior to 9 months of isoniazid alone for preventing TB in HIV-infected patients [33]. Notably, no hypersensitivity reactions were reported in that study [33]. All of these studies suggest that a different dosing schedule, frequent administration (twice-weekly or daily) with a lower dose of rifapentin (maximum dose of 600 mg) and isoniazid (maximum dose of 300–600 mg), could possibly result in equivalent prevention with fewer serious adverse events including flu-like syndrome or anaphylaxis. Further study is needed to elucidate this issue.
- Although our research had the advantage of being conducted for a homogenous population of HCWs, there were several limitations. First, the 3HR group received treatment in a self-administered manner and their adverse events were collected retrospectively, while the adverse events were prospectively collected under DOT in the 3H₁P₁ group. This difference might have led to the lower treatment completion rate and lower frequency of adverse events noted in the 3HR group. If the 3HR group had received DOT, it is possible that the treatment completion rate might have been higher. Also, some adverse events, especially the milder ones, were likely not reported in the 3HR group. Second, anaphylaxis was not confirmed in three of the four subjects by means of an IgE-mediated skin test.
- In conclusion, South Korean HCWs with LTBI treated with the 3H₁P₁ regimen had a higher treatment completion rate and less hepatotoxicity when compared with those receiving the 3HR regimen. However, treatment with the 3H₁P₁ regimen resulted in a higher rate of SDR such as flu-like syndromes and a 1.8% rate of anaphylaxis. These findings suggest that the 3H₁P₁ regimen might not be appropriate for widespread use among the general population with LTBI in South Korea. However, since the rifapentine containing regimen has advantages in terms of short treatment duration and low hepatotoxicity, it could be used cautiously in selected population with LTBI, such as the elderly with a risk for hepatotoxicity. Further study with a different dosage or dosing schedule of rifapentine is worthwhile, as this modified regimen could possibly have a lower rate of adverse events.
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- ## Declaration of competing interest
- None declared.
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- ## Appendix A. Supplementary data
- Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.10.005>.
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Online Data Supplement

Adverse events and treatment completion rates of a 12-dose weekly isoniazid and rifapentine course for healthcare workers in South Korea

Rifapentine skin test

One tablet of rifapentine[®] (150 mg) was diluted in physiological saline (NaCl, 0.9%) at a concentration of 0.02 mg/mL. Dilutions of 0.02, 0.002, and 0.0002 mg/mL of rifapentine were administered intradermally on the upper back by one investigator (Hyouk-Soo Kwon) with a 1-mL syringe and a 26-gauge needle. Saline and histamine (0.1 mg/mL) were used for negative and positive controls, respectively. The area of the wheal was measured after 20 min. A positive skin test for rifapentine was defined as a wheal greater than 3 mm. Results of subjects 1 were as follows:

	Wheal	Flare
Saline	0	0
Histamine	6 mm	25 mm
Rifapentine, 0.02 mg/mL	9 mm	25 mm
Rifapentine, 0.002 mg/mL	12 mm	25 mm
Rifapentine, 0.0002 mg/mL	9 mm	25 mm