Impact of Age on Outcome of Rifapentine-Based Weekly Therapy for Latent Tuberculosis Infection

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Background. Weekly rifapentine and isoniazid (3HP) is gaining popularity for latent tuberculosis infection treatment because of its short course and high completion rate. Prior to widespread use, comprehensive 3HP treatment assessment covering an all-age population is essential.

Methods. Participants receiving ≥ 3HP dose from September 2014 to December 2019 were stratified into elderly (≥65 years), middle-aged (≥35 & <65 years), and younger (≤35 years) age groups. This study investigated the impact of age on treatment outcome, particularly systemic drug reactions (SDRs) and 3HP discontinuation.

Results. Overall, 134 of 579 (23.1%) participants were elderly. The completion rate was 83.1% overall and was highest and lowest in the younger group (94.5%) and elderly (73.9%) group, respectively. However, the 3HP discontinuation rate was not significantly different among the 3 groups in multivariate logistic regression analysis. In total, 362 (62.5%) participants experienced 1 or more adverse drug reactions (ADRs), of which 38 (10.5%) and 98 (27.1%) required temporary and permanent treatment interruption, respectively. The SDR risk was 11.2% in overall and 17.1% in the middle-aged group, 3.04-fold higher than that in the elderly group (P = .025). This finding was consistently observed in different clinical settings. Hypertensive events accompanied with flu-like symptoms occurred in 11.2% of elderly participants, and accounted for 50% of grade ≥3 ADRs.

Conclusions. With proper medical support and programmatic follow-up, the 3HP completion rate is >70% even in elderly participants. In middle-aged and elderly individuals, 3HP should be employed with caution because of risk of SDRs and hypertensive events, respectively.

Keywords. age; hypertension; latent tuberculosis infection; rifapentine; systemic drug reaction.

Latent tuberculosis infection (LTBI) is an asymptomatic immunological state of heightened subsequent risk of active tuberculosis (TB). Approximately one-fourth of the global population is estimated to have LTBI [1]. Hence, to achieve the goals of the End TB strategy by 2035, treatment for LTBI is regarded as an irreplaceable component of public health policy.

Aging has been recognized to increase the risk of active TB [2]. In Taiwan, a country with an intermediate incidence of TB, the incidence of TB among individuals older than 65 years was 273.61 per 100 000 in 2018, which was 6.6-fold higher than that in the general population. This age group also accounts for 57.4% of all TB cases and 83% of TB-related deaths [3]. Therefore, LTBI interventions may be more critical for this TB-vulnerable group than other age groups.

LTBI treatment has evolved over decades. A short-course regimen termed 3HP, comprising once-weekly high-dose rifapentine (RPT) plus isoniazid (INH) for a total 12 doses, is currently gaining popularity for LTBI treatment because its completion rate approaches 90% [4, 5] and it is as effective as [5–7] and less hepatotoxic (0%–1.5% vs 1.2%–5.3%) [4, 7–11] than 9-month daily INH (9H). However, approximately half of subjects receiving 3HP experience adverse drug reactions (ADRs; defined as any unintended, harmful events attributed to the normal use of study drugs [12]). Most reported ADRs are self-limited, with <5% being severe (grade 3 or higher) [4, 13]. However, during 3HP treatment, 2%–10% of subjects experience a systemic drug reaction (SDR), defined as either (1) hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis; or (2) >4 flu-like symptoms,
with >1 being grade 2 or higher [11]. Occurrence of SDRs almost always leads to treatment interruption or termination [4, 5, 14].

The risk of SDR is a considerable concern in the elderly population because data from the PREVENT TB (Three Months of Weekly Rifapentine and Isoniazid for M. Tuberculosis Infection ClinicalTrials.gov number, NCT00023452) demonstrated that age >35 years was associated with increased SDR risk [11]. However, the relatively young age (median 36 years) and healthy status of these study participants precluded a detailed examination of the impact of age on the outcomes of 3HP treatment. Safety reports on the use of 3HP in geriatric populations remain limited.

With the gradual implementation of public health policy under the National TB Program of Taiwan, the screening and treatment of LTBI have expanded to cover all-age TB contacts and high-risk populations. This study aimed to comprehensively assess the outcomes of 3HP in an all-age population, with special emphasis on the age effect, to provide evidence and guidance for further widespread use of this regimen.

METHODS

Study Design

The eligible participants in the current study were prospectively recruited, in collaboration with public health professionals, from 2 medical centers with their 3 affiliated hospitals and 2 regional hospitals between September 2014 and December 2019. The study was approved by the institutional ethics committees (see Supplementary Data for details). Written informed consent was obtained from all participants and legal representatives if they were incapacitated.

Study Population

Individuals were eligible for enrollment if they were aged ≥18 years. In accordance with public health policy on LTBI intervention in Taiwan, this study recruited individuals in close contact with patients who had acid-fast bacilli (AFB) smear- or culture-positive pulmonary TB; people with high TB risk as defined by the World Health Organization [15], such as workers and residents in healthcare facilities; and patients with poorly controlled diabetes, who had ≥1 result of glycated hemoglobin level >9.0% within 1 year prior to enrollment. All participants were positive for LTBI by using QuantiFERON-TB Gold In-Tube (QFT; Cellestis/Qiagen, Carnegie, Australia), and received ≥1 dose of 3HP. Participants were stratified into 3 age groups (elderly group: ≥65 years; middle-aged group: >35 years & <65 years; younger group: ≤35 years).

Patients were excluded if they had a history of TB, ever received treatment for LTBI, were confirmed or suspected cases of active TB, and had a contraindication for INH or RPT administration.

Programmatic Management During LTBI Treatment and Occurrence of ADRs

The participants received 3HP (see Supplementary Data for details) under supervision by government-paid directly observed therapy (DOT) supporters. Acetaminophen was prescribed and recommended to be taken as needed at the first visit. Within 2 days after each dose of 3HP and at the time ADRs were reported, ADRs were assessed through a phone interview (preferred option) or Line mobile app with permission from participants by TB case managers in hospitals and DOT supporters in the community; all were trained and qualified by the Taiwan Centers for Disease Control. Caregivers assessed the ADRs of subjects with disability living in healthcare facilities through regular physical monitoring (3 times daily), including vital sign measurement and a systemic manifestation record (see Supplementary Table 1) for 48 hours after each dose of 3HP treatment.

A blood test was performed at baseline, monthly after treatment, or during SDR development (see Supplementary Data for details). Once any ADR was identified by public health or medical personnel or self-reported by participants, the case managers, DOT supporters, or caregivers reported and discussed with primary care physicians who would then determine the causal relationship between the ADR and 3HP treatment by using Naranjo score [16]. Only probable and definite ADRs with Naranjo score ≥5 points were finally analyzed. Medical advice was provided based on the severity of the ADR [17], including close monitoring, symptomatic treatment, and arrangement of a hospital visit if necessary.

Adverse drug reactions were defined as unintended, harmful events attributed to the normal use of medicines [12]. All types of ADR were not mutually exclusive and were counted in each corresponding category. Two phenotypes were both considered as SDRs [11]: (1) hypotension (systolic blood pressure <90 mm Hg), urticaria, angioedema, acute bronchospasm, or conjunctivitis; and (2) >4 of the following flu-like symptoms occurring concurrently, with >1 being grade 2 or higher in severity: weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, and chills. Clinically significant hepatotoxicity was defined as aspartate aminotransferase and/or alanine aminotransferase ≥3 upper limit of normal (ULN) or total bilirubin ≥2 ULN [18].

All participants were followed up until premature termination, development of active TB, or 1 week after treatment completion.

Assessment of Objectives

The primary objective was to compare the treatment outcomes, including treatment completion rate and risk of SDR in different age groups. Completion of 3HP was defined as completing 12 doses within 16 weeks (4 months), and each dose had to be taken at least 5 days apart [19].
Statistical Analysis
The demographic data, comorbidity status, characteristics of TB exposure, smoking status, chest radiographic and laboratory data before 3HP treatment, and outcome of 3HP treatment were collected in a structured digital file.

Intergroup differences were analyzed using the \( \chi^2 \) test or Fisher exact test for categorical variables, and 1-way analysis of variance, Kruskal-Wallis test, or Mann-Whitney \( U \) test for continuous variables depending on the normality. Multivariate logistic regression was used to calculate the adjusted odds ratio (aOR), 95% confidence intervals (95% CIs), and \( P \) values for potential risk factors. A 2-sided \( P \) value <.05 was considered statistically significant and the significance was assessed following Bonferroni correction for multiple comparisons. All analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, Illinois).

RESULTS
Study Population
Figure 1 illustrates the process of participant selection. During the study period, a total of 1021 QFT-positive cases were interviewed for LTBI treatment. Among them, 579 participants, including 165 (28.5%) in the younger group, 280 (48.4%) in the middle-aged group, and 134 (23.1%) in the elderly group were recruited for further analysis.

Clinical Characteristics of the Study Population
The clinical characteristics of the participants are shown in Table 1. Among the 579 subjects, 46.8% were male, 78.4% had never smoked, and 76.5% were TB close contacts. Abnormal chest radiographic findings unrelated to pulmonary TB were identified in 16.2% of the participants. The 443 TB close contacts belonged to 286 index TB cases. Of the index cases, 65.7% were male and 93.3% were sputum smear positive for AFB (Supplementary Table 2). The household (26.6%) and the workplace (20.4%) were the most common exposure settings.

The elderly group had significantly higher proportions of systemic comorbidities and abnormal chest radiographic findings than other groups. Among the elderly group, 55.2% were noncontacts. The baseline characteristics were similar between contacts and noncontacts, except the prevalence of DM, cerebrovascular accident, and dementia (Supplementary Table 3). More participants in the middle-aged group had household (33.6%) and workplace exposure (30.7%), whereas more elderly participants had healthcare-related exposure (14.2%). The middle-aged group had a significantly stronger QFT response, defined as the difference in interferon-\( \gamma \) level between antigen and nil tubes, than the younger group (\( P < .001 \) by post hoc analysis), and a slightly but insignificantly higher QFT response than the elderly group (\( P = .600 \) by post hoc analysis).

Treatment Course and Outcome
The treatment courses and outcomes are summarized in Table 2. A total of 481 (83.1%) of the participants completed 3HP treatment. The younger group had the highest treatment completion rate (94.5%), and the elderly group had the lowest (73.9%). Among all participants, 38 (6.6%) experienced an ADR requiring transient treatment interruption. In contrast to the other groups, the younger group experienced more ADRs but had no consequential treatment interruption (\( P < .001 \)). For the participants with transient interruption of 3HP treatment, SDR was most common in the middle-aged group (\( P = .015 \); Supplementary Table 4).

Overall, the permanent discontinuation rate of 3HP was 16.9%, being most common in the elderly group (26.1%) and least common in the younger group (5.5%; Table 2). The number of doses before 3HP discontinuation was 4.3 ± 2.2, not significantly different among the 3 age groups. SDR was the most common reason for discontinuation in the middle-aged group (9.6% vs 2.4% in the younger group and 4.5% in the elderly group; \( P = .014 \)).

Permanent discontinuation of 3HP due to hepatotoxicity was more common in the elderly (4.5%) and middle-aged (4.3%) groups than the younger group (0%; \( P = .025 \); Table 2). Although the elderly group had a significantly higher risk of ADRs other than SDR and hepatotoxicity (\( P = .004 \)), 85% (46 of 54; Table 3) of the ADRs were self-limited or well-tolerated (grade 1 and 2). Active TB was confirmed in 2 (1.5%) participants in the elderly group and none in the other 2 groups (\( P = .036 \); Table 2).
Details of ADRs

Of the 579 participants, 362 (62.5%) reported at least 1 ADR during treatment. The details of these ADRs are provided in Table 3 and Supplementary Table 5. The overall risk of SDR was 11.2%, and this risk was highest (17.1%) in the middle-aged group (elderly group: 6.7%; younger group: 4.8%; P < .001).

In terms of individual symptoms of SDR, the middle-aged group had the highest risk of flu-like syndrome and urticaria.
Hypotension occurred in 1.7% of the overall population and was more common, although nonsignificantly, in the middle-aged group (2.5%).

Liver function impairment occurred in 32 (5.5%) participants in the total study population and had a nonsignificantly different incidence between the 3 age groups. Only 7 (1.2%) participants experienced clinically significant hepatotoxicity. Clinically nonsignificant upward trends of hepatic aminotransferases and total bilirubin were observed during treatment in the middle-aged group (Supplementary Table 6).

The elderly group had higher risk of grade ≥3 ADRs other than SDR and hepatotoxicity than the other groups (6.0% vs 1.2% in the younger group and 1.8% in the middle-aged group; P = .018), and these ADRs were mainly hypertensive events (50%; Table 3). During treatment, 22 participants (3.8%; Supplementary Table 7) experienced a hypertensive event accompanied by flu-like related symptoms; this was significantly more common in the elderly group (11.2%; P < .001; Table 3).

The risk of a hypertensive event was significantly higher among the participants with underlying hypertension than among those without hypertension in both the elderly (16% [14/86] vs 2% [1/48]; P = .012) and middle-aged (8% [5/63] vs 1% [2/217]; P = .007) groups (Tables 3 and 4).

Most hypertensive events occurred 8 hours after the third dose, with a mean elevation in blood pressure of 26 mm Hg (interquartile range, 20–37 mm Hg), and persisted for a median duration of 1 day (Table 4). All 22 participants experienced hypertensive events again after the next 3HP dose. Three of them discontinued 3HP thereafter, and the others completed treatment by temporary modification of antihypertensive drugs after each 3HP dose.

Upper gastrointestinal symptoms were more commonly reported in the elderly group (41.8%; P = .012) (Table 3). No deaths or long-term sequela were observed.

**Impact of Age on SDR**

Multivariate logistic regression analysis revealed that middle age was significantly associated with increased SDR risk during 3HP treatment in comparison with being elderly (aOR, 3.04 [95% CI: 1.15–8.03], P = .025 in overall population; 6.48 [95% CI: 1.29–32.68], P = .024 in those with contact history; Supplementary Table 8). Subgroup analyses revealed that this finding was consistently observed in most clinical settings (Supplementary Figure 1, upper panels). The risk of SDR was not different between the elderly and younger groups.

**Impact of Age on the Discontinuation of 3HP**

Multivariate logistic regression analysis revealed that risk of treatment discontinuation was similar in the middle-aged and elderly groups (aOR, 1.02 [95% CI: .51–2.03], P = .963 in overall population; 1.02 [95% CI: .40–2.60], P = .963 in those with contact history; Supplementary Table 9). In comparison with the elderly group, the younger group had slightly but nonsignificantly lower risk of treatment discontinuation (aOR, 0.38 [95% CI: .13–1.16], P = .089 in the overall population; aOR, 0.38 [95% CI: .09–1.57], P = .182 in those with contact history). Subgroup analyses demonstrated the consistent findings in most clinical settings (Supplementary Figure 1, lower panels).

**DISCUSSION**

This study obtained 3 major findings. First, a high completion rate of 3HP treatment can be achieved in elderly people...
(73.9%) in a variety of clinical subpopulations under a programmatic setting. Second, special attention must be paid to the development of hypertensive events in elderly patients, particularly those with underlying hypertension. Third, middle-aged subjects, but not younger or older subjects, have a high risk of SDR (17.1%). The exact mechanisms remain to be determined.

In a postmarketing surveillance report [20], the 3HP completion rate was inversely proportional to age. Compared with subjects aged between 31 and 44 years, the elderly group had a 1.72-fold higher risk of discontinuation. However, the safety profile of 3HP in different age groups remains lacking. A randomized controlled study on 3HP enrolling participants between 50 and 70 years old in China was prematurely terminated because approximately one-fifth of the participants experienced intolerable ADRs [21]. Possible explanations are age effect and the use of generic drugs.

The completion rate of elderly participants in this study was 73.9% even when 56.7% of participants experienced ≥1 ADR, indicating that in a programmatic setting with supervised treatment, careful ADR monitoring, and management, 3HP can still be implemented in elderly subjects safely. Elderly people are particularly susceptible to ADRs because they have multiple comorbidities, polypharmacy, and impaired physical function [22].

One finding of the present study that requires further attention is that 1 of 9 elderly participants developed a hypertensive event, which was not observed in younger or middle-aged participants. This finding suggests the need for careful monitoring and management of ADRs in elderly patients to ensure the safe implementation of 3HP.

### Table 3. Details of Adverse Drug Reactions

| Adverse Reaction | Total (N = 579) | Age ≤35 y (n = 165) | 35 y < age <65 y (n = 280) | Age ≥65 y (n = 134) | P Value |
|------------------|-----------------|---------------------|---------------------------|-----------------|---------|
| SDR | 65 (11.2) | 8 (4.8) | 48 (17.1) | 9 (6.7) | <.001 |
| Flu-like syndrome | 47 (8.1) | 6 (3.6) | 34 (12.1) | 7 (5.2) | .003 |
| Hypotension | 10 (1.7) | 2 (1.2) | 7 (2.5) | 1 (0.7) | .367 |
| Urticaria | 6 (1.0) | 0 (0) | 6 (2.1) | 0 (0) | .039 |
| Conjunctivitis | 4 (0.7) | 0 (0) | 3 (1.1) | 1 (0.7) | .418 |
| Hepatotoxicity | 32 (5.5) | 6 (3.6) | 19 (6.8) | 7 (5.2) | .367 |
| AST, ALT >5 ULN or TBil >3 mg/dL | 7 (1.2) | 0 (0) | 6 (2.1) | 1 (0.7) | .116 |
| AST, ALT >3 ULN or TBil >2 mg/dL | 18 (3.1) | 5 (3.0) | 11 (3.9) | 2 (1.5) | .409 |
| AST, ALT >2 ULN | 7 (1.2) | 1 (0.6) | 2 (0.7) | 4 (3.0) | .700 |
| ADR except SDR and hepatotoxicity | 266 (45.9) | 92 (55.8) | 120 (42.9) | 54 (40.3) | .010 |
| Grade ≥3 | 15 (2.3) | 2 (1.2) | 5 (1.8) | 8 (6.0) | .018 |
| Hypertensive event | 5 (0.9) | 0 (0) | 1 (0.4) | 4 (3.0) | .009 |
| Grade 2 | 103 (17.8) | 20 (12.1) | 56 (20.0) | 27 (20.1) | .102 |
| Individual symptom* | | | | | |
| Flu-like symptoms | | | | | |
| Malaise and lethargy | 261 (45.1) | 60 (36.4) | 136 (48.2) | 66 (49.3) | .036 |
| Febrile sensation and flush | 81 (14.0) | 15 (9.1) | 50 (17.9) | 16 (11.9) | .025 |
| Fever | 147 (25.4) | 26 (15.8) | 87 (31.1) | 34 (25.4) | .002 |
| Dizziness | 184 (31.8) | 31 (18.8) | 111 (39.6) | 42 (31.3) | <.001 |
| Headache | 158 (27.3) | 33 (20.0) | 101 (36.1) | 24 (17.9) | <.001 |
| Chills | 85 (14.7) | 10 (6.1) | 59 (21.1) | 16 (11.9) | <.001 |
| Myalgia and arthralgia | 138 (23.8) | 23 (13.9) | 92 (32.9) | 23 (17.2) | <.001 |
| URT symptoms | 87 (15.0) | 22 (13.3) | 51 (18.2) | 14 (10.4) | .081 |
| Dyspnea | 34 (5.9) | 6 (3.6) | 20 (7.1) | 8 (6.0) | .316 |
| Gastrointestinal disorders | | | | | |
| UGI symptoms | 199 (34.4) | 42 (25.5) | 101 (36.1) | 56 (41.8) | .012 |
| Diarrhea | 28 (4.8) | 5 (3.0) | 17 (6.1) | 6 (4.5) | .341 |
| Cutaneous reactions | 101 (17.4) | 21 (12.7) | 60 (21.4) | 20 (14.9) | .042 |
| Cardiovascular | | | | | |
| Palpitation | 35 (6.0) | 7 (4.2) | 22 (7.9) | 6 (4.5) | .200 |
| Hypertension | 22 (3.8) | 0 (0) | 7 (2.5) | 15 (11.2) | <.001 |
| Conjunctivitis or increase discharge | 31 (5.4) | 8 (4.8) | 15 (5.4) | 8 (6.0) | .912 |

Data are presented as No. (%). The denominator of each calculation of percentage is the case number of each corresponding age group.

Abbreviations: ADR, adverse drug reaction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; SDR, systemic drug reaction; UGI, upper gastrointestinal; ULN, upper limit of normal; URT, upper respiratory tract.

*One of the participants with SDR had conjunctivitis, urticaria, and flu-like syndrome simultaneously.

*One participant experienced hypotension (lowest blood pressure: 81/65 mm Hg) with tachycardia (highest heart rate: 126 beats per minute), and another experienced urticaria with fever.

*Including flu-like syndrome (n = 2), concomitant flu-like symptoms and cutaneous reaction (n = 1), hypotension (n = 1; lowest blood pressure: 85/57 mm Hg), and hypertensive event with severe dizziness and nausea (n = 1; highest blood pressure: 186/155 mm Hg).

*Including hypertensive event (n = 2), hypertensive crisis with transient ischemic attack (n = 1), concomitant hypertensive event and aspiration pneumonia (n = 1), concomitant aspiration pneumonia and gastrointestinal bleeding (n = 1), gastrointestinal bleeding (n = 1), flu-like symptoms (n = 1), and paroxysmal atrial fibrillation (n = 1).

*ADRs with an incidence of <5% are shown in Supplementary Table 5.
Table 4. Clinical Characteristics of the 22 Participants Experiencing a Hypertensive Event During 12-Dose Weekly Isoniazid and Rifapentine Treatment, Stratified by Age

| Characteristic                      | Total (N = 22) | 35 y < age <65 y (n = 7) | Age ≥65 y (n = 15) | P Value |
|------------------------------------|----------------|--------------------------|-------------------|---------|
| Male sex                           | 13 (59)        | 4 (57)                   | 9 (60)            | .899    |
| Age, y, median (IQR)               | 71 (63–79)     | 60 (58–63)               | 76 (71–83)        | <.001a  |
| Hypertension history               | 19 (86)        | 5 (71)                   | 14 (93)           | .163    |
| Anti-hypertensive drugs            |                |                          |                   |         |
| ACEI/ARB                           | 13 (59)        | 2 (29)                   | 11 (73)           | .047    |
| β-blocker                          | 7 (32)         | 1 (14)                   | 6 (40)            | .228    |
| CCB                                | 17 (77)        | 4 (57)                   | 13 (87)           | .124    |
| Diuretics                          | 8 (36)         | 1 (14)                   | 7 (47)            | .141    |
| INH dose, mg/kg, median (IQR)      | 15 (13–17)     | 16 (14–18)               | 15 (13–17)        | .490*   |
| RPT dose, mg/kg, median (IQR)      | 15 (14–17)     | 16 (14–17)               | 15 (13–17)        | .783*   |
| Onset dose, median (IQR)           | 3 (2–3)        | 2 (2–5)                  | 3 (1–3)           | .581    |
| Onset after dosing, h, median (IQR)| 8 (6–12)       | 8 (6–12)                 | 8 (5–10)          | .490    |
| Duration, d, median (IQR)          | 1 (0.5–1)      | 1 (1–1.5)                | 1 (0.5–1)         | .185    |
| Max MBP change, mm Hg, median (IQR)| 26 (20–37)     | 20 (19–37)               | 32 (23–37)        | .210*   |
| Grade ≥3                           | 3 (14)         | 1 (14)b                  | 2 (13)c           | >.999   |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; INH, isoniazid; IQR, interquartile range; MBP, mean blood pressure; RPT, rifapentine.

* Mann-Whitney U test was used to calculate the P value.

event, which accounted for half of the grade ≥3 ADRs other than SDR and hepatotoxicity. The hypertensive event might be attributable to drug–drug interactions between antihypertensive agents and RPT, which is an inducer of cytochrome P450 to accelerate the metabolism of calcium channel blockers, β-blockers, and angiotensin receptor blockers [23]. Renal function impairment is another possible explanation, as 17% of an administered dose of RPT is excreted through the kidneys [24]. A retrospective study analyzing 37 adults with end-stage renal disease demonstrated that 22% developed severe hypertension (≥180/110 mm Hg) during the first 6 weeks of 3HP treatment [25]. The impaired renal clearance due to aging may result in a higher serum RPT level [14] and thus attenuate the effect of antihypertensive drugs.

The finding that one-sixth of the middle-aged group in the present study experienced SDR during 3HP treatment is unexpected. Although some reports suggest that RPT is the offending drug causing SDR [11, 26, 27], the results of 2 recent studies revealed that the N-acetyl transferase 2 genotype and plasma concentration of INH are associated with the development of SDR [14, 28], implying that INH may play a critical role in the pathophysiology of 3HP-related SDR. Although the risk of SDR during 3HP treatment is higher in individuals older than 35 years [4, 11], results of the current study demonstrate that SDR risk does not increase further in elderly people. A previous report also revealed that patients aged between 30 and 65 years experienced more flu-like symptoms due to either INH or rifamycin during active TB and LTBI treatment [14].

The reason for the high risk of SDR in the middle-aged group is unknown. Middle age can be the period of greatest psychological, behavioral, and social stress during a lifespan [29]. Stress and allergies are mutually reinforcing. Stress mediates inflammation by releasing cytokines, including histamine, to initiate or aggravate allergic reactions [30, 31], which may have contributed to the higher incidence of SDR in the middle-aged group. Age-dependent immunosenescence, which refers to the gradual deterioration of a person’s immune system [32], probably explains the lower SDR occurrence among elderly patients in the current study. Further studies are necessary to confirm this finding and explore the underlying pathophysiology.

This study has some limitations. First, some participants were unable to report symptoms reliably due to dementia or other comorbidities. This may have affected the accuracy of ADR registration. Second, the diagnosis of LTBI was determined using QFT positivity, and the sensitivity of QFT was shown to decrease with increasing age [33]. Third, the high completion rate despite of the high rate of ADRs might be partly due to an aggressive programmatic approach that closely integrated public health and medical professionals. Such resources are not always available in other countries and thus outcomes of LTBI intervention may vary.

In conclusion, this study provides information regarding the safety of 3HP in different age groups and clinical settings. Under proper medical support and with programmatic follow-up, the completion rate of 3HP is high, even for elderly patients.
Caution should be exercised during 3HP treatment due to the higher risk of SDR occurrence in middle-aged patients and hypertensive events in elderly individuals.

Notes

Author contributions. H.-L. H., J.-Y. W., and I.-W. C. designed the study. H.-L. H., M.-R. L., M.-H. C., P.-L. L., C.-K. H., C.-C. S., P.-C. L., and T.-C. C. collected the data and performed the database analysis. H.-L. H. and M.-R. L. contributed to the statistical analysis. H.-L. H., M.-R. L., and J.-Y. W. contributed to data interpretation and prepared the first draft of the manuscript. M.-R. L., M.-H. C., P.-L. L., and I.-W. C. critically revised the draft manuscript. J.-Y. W. was responsible for coordination. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016; 13:e1002152.
2. Byng-Maddick R, Noursadeghi M. Does tuberculosis threaten our ageing populations? BMC Infect Dis 2016; 16:119.
3. Taiwan Centers for Disease Control. Taiwan tuberculosis control report, 2016, 2018. Available at: https://www.cdc.gov.tw/InfectionReport/Info/uKm0f0HV5mkNaX09NY-rQtmfId-OGFtEHrCaaPSKME03dAzA. Accessed 7 January 2021.
4. Sun HY, Huang YW, Huang WC, et al. Twelve-dose weekly rifapentine plus isoniazid for latent tuberculosis infection: a multicenter randomized controlled trial in Taiwan. Tuberculosis (Edinb) 2018; 111:121–6.
5. Sterling TR, Villarino ME, Borisov AS, et al; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365:2155–66.
6. Martinson NA, Barnes GL, Meulien LH, et al. New regimens to prevent tuberculosis in program settings with 12-dose weekly isoniazid and rifapentine for latent Mycobacterium tuberculosis infection. Clin Infect Dis 2017; 65:1085–93.
7. Sandul AL, Nwana N, Holcombe JM, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine for latent tuberculosis infection. JAMA Intern Med 2016; 176:1576–85.
8. Martinson NA, Barnes GL, Meulien LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011; 365:11–20.
9. Schechter M, Zajdenverg R, Falco G, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006; 173:922–6.
10. Bellknap R, Holland D, Feng PJ, et al; TB Trials Consortium iAdhere Study Team. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. Ann Intern Med 2017; 167:689–97.
11. Njie GJ, Morris SB, Woodruff RY, Moro RN, Vernon AA, Borisov AS. Isoniazid-rifapentine for latent tuberculosis infection: a systematic review and meta-analysis. Am J Prev Med 2018; 55:244–52.
12. Simkins J, Abbo LM, Camargo JE, Rosa R, Morris ML. Twelve-week rifapentine plus isoniazid versus 9-month isoniazid for the treatment of latent tuberculosis in renal transplant candidates. Transplantation 2017; 101:1468–72.
13. Sterling TR, Moro RN, Borisov AS, et al; Tuberculosis Trials Consortium. Flu-like and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT tuberculosis study. Clin Infect Dis 2015; 61:527–35.
14. Lee MR, Huang HL, Lin SW, et al. Isoniazid concentration and NAT2 genotype predict risk of systemic drug reactions during 3HP for LTBI. J Clin Med 2019; 8:812.
15. World Health Organization. Guidelines on the management of latent tuberculosis infection. 2015. Available at: https://www.who.int/tb/publications/lntuberculosis-infection/en/. Accessed 7 January 2021.
16. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30:239–45.
17. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, version 2.0. 2014. Available at: https://rsc.niaid.nih.gov/sites/default/files/daisd-ad-grading-table-v2-nov2014.pdf. Accessed 7 January 2021.
18. Tajiri K, Shimizu Y. Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol 2008; 14:6774–85.
19. Taiwan Centers for Disease Control. Clinical recommendations for the treatment of latent tuberculosis infection using 3HP. 2016. Available at: https://www.cdc.gov.tw/Uploads/4d4d6b6b-e233-49e9-8dee-de5ca8e7c20b.pdf. Accessed 7 January 2021.
20. Sandul AL, Nwana N, Holcombe JM, et al. High rate of treatment completion in program settings with 12-dose weekly isoniazid and rifapentine for latent tuberculosis infection. Clin Infect Dis 2017; 65:1085–93.
21. Gao L, Zhang H, Xin H, et al. Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: a randomized controlled trial. Eur Respir J 2018; 52:180147T.
22. Parameswaran Nair N, Chalmers L, Peterson GM, Bereznicki BJ, Castelino RL, Bereznicki LR. Hospitalization in older patients due to adverse drug reactions— the need for a prediction tool. Clin Interv Aging 2016; 11:497–505.
23. Baciewicz AM, Chrisman CR, Finch CK, Self TH. Update on rifampin, rifabutin, and rifapentine drug interactions. Curr Med Res Opin 2013; 29:1–12.
24. Bridgewater N. Priftin (rifapentine) tablets [prescribing information]. 1998. Available at: https://www.accessdata.fda.gov/drugsatmdocs/label/2010/021024s009lbl.pdf. Accessed 7 January 2021.
25. Simkins J, Morris MI, Abbo LM, Camargo IF. Severe hypertension after initiation of rifapentine/isoniazid for latent tuberculosis in renal transplant candidates. Transpl Int 2017; 30:108–9.
26. Controlled trial of intermittent regimens of rifampin plus isoniazid for pulmonary tuberculosis in Singapore. The results up to 30 months. Am Rev Respir Dis 1977; 116:807–20.
27. Dickinson JM, Mitchison DA, Lee SK, et al. Serum rifampicin concentration related to dose size and to the incidence of the ‘flu’ syndrome during intermittent rifampicin administration. J Antimicrob Chemother 1977; 3:445–52.
28. Yu Y-T, Tsao S-M, Yang W-T, et al. Association of drug metabolic enzyme genetic polymorphisms and adverse drug reactions in patients receiving rifapentine and isoniazid therapy for latent tuberculosis. Int J Environ Res Public Health 2020; 17:210.
29. Graham JE, Christian LM, Kickeit-Glaser JK. Stress, age, and immune function: toward a lifespan approach. J Behav Med 2006; 29:389–400.
30. De Martinis M, Sirufo MM, Ginaldi L. Allergy and aging: an old/new emerging health issue. Aging Dis 2017; 8:62–75.
31. Simon AK, Holland GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 2015; 282:20143085.
32. Barranco P, López-Serrano MC. Evolution of the immune system in human adults from infancy to old age. Proc Biol Sci 2015; 282:20143085.
33. Chien YJ, Chiang HT, Lu MC, et al. QuantiFERON-TB Gold Plus is a more sensitive screening tool than QuantiFERON-TB Gold In-Tube for latent tuberculosis infection among older adults in long-term care facilities. J Clin Microbiol 2018; 56:e00427-18.