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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 ≥1 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,

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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 χ^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.

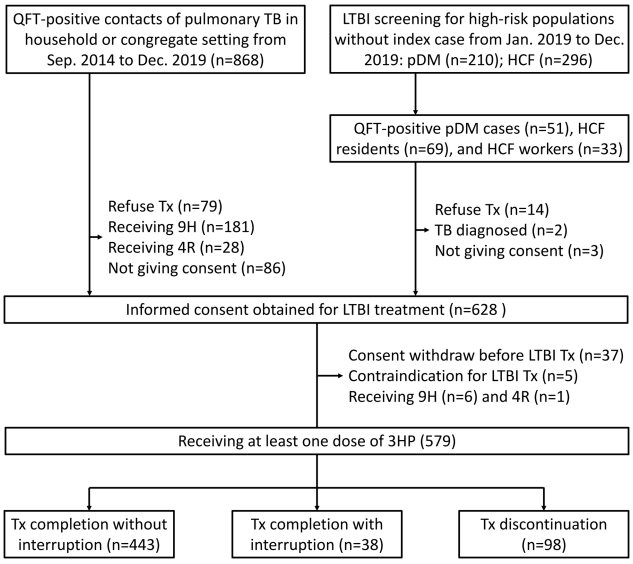

Figure 1. Case selection process. Abbreviations: 3HP, weekly rifapentine and isoniazid therapy for 12 doses; 4R, daily rifampin therapy for 4 months; 9H, daily isoniazid therapy for 9 months; HCF, healthcare facility; LTBI, latent tuberculosis infection; pDM, poorly controlled diabetes mellitus; QFT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis; Tx, treatment.

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 accidence, 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-γ 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).

Table 1. Clinical Characteristics of the 579 Participants Receiving 12-Dose Weekly Isoniazid and Rifapentine Treatment at Baseline, Stratified by Age

Characteristic	Total (N = 579)	Age ≤ 35 y (n = 165)	35 y < age <65 y (n = 280)	Age ≥65 y (n = 134)	*P* Value
Male sex	271 (46.8)	92 (55.8)	113 (40.4)	66 (49.3)	.006
BMI, kg/m^2, mean ± SD	23.9 ± 3.9	22.9 ± 3.9	24.4 ± 3.5	23.9 ± 3.9	<.001
<18.5	37 (6.4)	16 (9.7)	8 (2.9)	13 (9.7)	.003
≥30	41 (7.1)	12 (7.3)	16 (5.7)	13 (9.7)	.332
Smoking status					<.001
Never smoker	454 (78.4)	144 (87.3)	202 (72.1)	108 (80.6)	
Ex-smoker	53 (9.2)	2 (1.2)	38 (13.6)	18 (13.4)	
Current smoker	72 (12.4)	19 (11.5)	45 (16.1)	8 (6.0)	
Systemic comorbidities					
Hypertension	151 (26.1)	2 (1.2)	63 (22.5)	86 (64.2)	<.001
Diabetes mellitus	105 (18.1)	0 (0)	44 (15.7)	61 (45.5)	<.001
Old cerebrovascular accidence	42 (7.3)	0 (0)	4 (1.4)	38 (28.4)	<.001
Chronic kidney disease, stage ≥3	41 (7.1)	0 (0)	10 (3.6)	31 (23.1)	<.001
End-stage renal disease	6 (1.0)	0 (0)	2 (0.7)	6 (4.5)	.002
Coronary artery disease	27 (4.7)	0 (0)	7 (2.5)	20 (14.9)	<.001
Congestive heart failure	24 (4.1)	0 (0)	6 (2.1)	18 (13.4)	<.001
Dementia	23 (4.0)	0 (0)	2 (0.7)	21 (15.7)	<.001
Atopy	22 (3.8)	3 (1.8)	11 (3.9)	8 (6.0)	.173
Autoimmune disease	8 (1.4)[a]	0 (0)	6 (2.1)	2 (1.5)	.173
Hepatitis B	27 (4.7)	3 (1.8)	16 (5.7)	8 (6.0)	.122
Hepatitis C	13 (2.2)	1 (0.6)	8 (2.9)	4 (3.0)	.243
Cancer	14 (2.4)[b]	2 (1.2)	4 (1.4)	8 (6.0)	.009
Peptic ulcer/GERD with antacid use	26 (4.5)	0 (0)	15 (5.4)	11 (8.2)	.002
QFT, IU/mL, mean ± SD					
Nil	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	0.2 ± 0.4	.436
Mitogen	8.8 ± 1.8	9.4 ± 1.5	9.0 ± 1.7	8.2 ± 2.1	<.001
TB antigen–Nil	2.3 ± 2.7	1.5 ± 2.4	2.7 ± 2.8	2.4 ± 2.5	<.001
Report of chest radiography					
Abnormal but not tuberculosis	94 (16.2)	7 (4.2)	35 (12.5)	52 (38.8)	<.001
TB close contact	443 (76.5)	156 (94.5)	227 (81.1)	60 (44.8)	<.001
Exposure setting					
Household exposure	154 (26.6)	26 (15.8)	94 (33.6)	34 (25.4)	<.001
Workplace exposure	118 (20.4)	25 (15.2)	86 (30.7)	7 (5.2)	<.001
Healthcare-related exposure	60 (10.4)	3 (1.8)	38 (13.6)	19 (14.2)	<.001
School exposure	111 (19.2)	102 (61.8)	9 (3.2)	0 (0)	<.001
Exposure intensity					
Same room	50 (8.6)	6 (3.6)	27 (9.6)	17 (12.7)	.015
Same house	320 (55.3)	127 (77.0)	161 (57.5)	32 (23.9)	<.001
Different house	73 (12.6)	23 (13.9)	39 (13.9)	11 (8.2)	.216
High-risk population without index case	136 (23.5)	9 (5.5)	53 (18.9)	74 (55.2)	<.001
Nursing home residents	62 (10.7)	3 (1.8)	12 (4.3)	47 (35.1)	<.001
Healthcare workers	30 (5.2)	6 (3.6)	21 (7.5)	3 (2.2)	.044
Poor diabetes control[c]	44 (7.6)	0 (0)	20 (7.1)	24 (17.9)	<.001
Drug dose, mg/kg, mean ± SD					
Isoniazid	14.0 ± 2.2	14.0 ± 2.4	14.0 ± 2.2	14.1 ± 2.0	.918
Rifapentine	14.1 ± 2.2	14.1 ± 2.4	14.1 ± 2.2	14.4 ± 2.0	.307

Data are presented as No. (%) unless otherwise indicated. The denominator of each calculation of percentage is the case number of each corresponding age group. χ^2 test and either 1-way analysis of variance or Kruskal-Wallis test, if appropriate, were used to calculate the *P* value for the differences among the 3 age groups.

Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; QFT, QuantiFERON-TB Gold In-Tube; SD, standard deviation; TB, tuberculosis.

[a]Three had rheumatoid arthritis, 2 had ankylosing spondylitis, and 1 each had autoimmune vasculitis, systemic lupus erythematosus, and autoimmune hepatitis.

[b]Seven had breast cancer, 2 had colon cancer, 2 had lung cancer, and 1 each had esophageal cancer, gastric cancer, and cervical cancer.

[c]Poor diabetes control was defined as ever having a glycated hemoglobin level >9.0% within the 1 year prior to enrollment.

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.

Table 2. Course and Outcome of 579 Participants Receiving 12-Dose Weekly Isoniazid and Rifapentine Treatment at Baseline, Stratified by Age

Course and Outcome	Total (N = 579)	Age ≤35 y (n = 165)	35 y < age <65 y (n = 280)	Age ≥65 y (n = 134)	*P* Value
Complete treatment	481 (83.1)	156 (94.5)	226 (80.7)	99 (73.9)	<.001
No ADRs	217 (37.5)	58 (35.2)	101 (36.1)	58 (43.3)	.280
Presence of ADR without Tx interruption	226 (39.0)	86 (52.1)	106 (37.9)	34 (25.4)	<.001
Presence of ADR with Tx interruption	38 (6.6)	12 (7.3)	19 (6.8)	7 (5.2)	.760
Permanent discontinuation	98 (16.9)	9 (5.5)	54 (19.3)	35 (26.1)	<.001
No. of doses before discontinuation, mean ± SD	4.3 ± 2.2	4.3 ± 2.3	4.4 ± 2.1	4.2 ± 2.4	.926
Cause of discontinuation					
SDR	37[a] (6.3)	4 (2.4)	27 (9.6)	6 (4.5)	.014
Hepatotoxicity	18 (3.1)	0 (0)	12 (4.3)	6 (4.5)	.025
ADRs except SDR/hepatotoxicity	29 (5.0)	5 (3.0)	10 (3.6)	14 (10.4)	.004
Withdraw consent	9 (1.6)	0 (0)	5 (1.8)	4 (3.0)	.106
Tuberculosis confirmed	2 (0.3)	0 (0)	0 (0)	2 (1.5)	.036
Other reasons	3[b] (0.5)	0 (0)	1 (0.4)	2 (1.5)	.177

Data are presented as No. (%) unless otherwise indicated. The denominator of each calculation of percentage is the case number of each corresponding age group. χ^2 test and either 1-way analysis of variance or Kruskal-Wallis test, if appropriate, were used to calculate the *P* value for the differences among the 3 age groups. The details of ADRs associated with discontinuation and the nature of SDRs are listed in Supplementary Table 3.

Abbreviations: ADR, adverse drug reaction; SD, standard deviation; SDR, systemic drug reaction; Tx, treatment.

[a]Among 37 participants with SDRs, the SDRs were flu-like syndrome in 22, hypotension in 10, conjunctivitis in 3, and urticaria in 4. One patient had flu-like syndrome, urticaria, and conjunctivitis simultaneously.

[b]One patient discontinued treatment because of repeated hospitalization during treatment, 1 died of sepsis, and 1 died of acute myocardial infarction.

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

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)[a]	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 T-Bil >3 mg/dL	7 (1.2)	0 (0)	6 (2.1)	1 (0.7)	.116
AST, ALT >3 ULN or T-Bil >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)	.100
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)[b]	5 (1.8)[c]	8 (6.0)[d]	.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[e]					
Flu-like symptoms					
Malaise and lethargy	261 (45.1)	60 (36.4)	135 (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; T-Bil, total bilirubin; SDR, systemic drug reaction; UGI, upper gastrointestinal; ULN, upper limit of normal; URT, upper respiratory tract.

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

[b]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.

[c]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).

[d]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).

[e]ADRs with an incidence of <5% are shown in Supplementary Table 5.

(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

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)	<.001[a]
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[a]
RPT dose, mg/kg, median (IQR)	15 (14–17)	16 (14–17)	15 (13–17)	.783[a]
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[a]
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.

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

[b]This patient had a 47 mm Hg elevation of MBP with severe dizziness and nausea after 12 hours of weekly isoniazid and rifapentine (3HP) use.

[c]One patient experienced a 74 mm Hg elevation of MBP with dizziness, malaise, and vomiting 10 hours after the third dose of 3HP. The highest recorded BP was 192/153 mm Hg, diagnosed as transient ischemic attack in the emergency department (18 hours after the fourth dose of 3HP). In another, 53 mm Hg elevation of MBP with nausea, vomiting, malaise, blurred vision, and palpitation was noted. The highest recorded BP was 183/147 mm Hg at 8 hours after the first dose of 3HP.

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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