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Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: a randomised controlled study

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A randomised controlled trial suggested that the short regimens tested for treatment of latent tuberculosis infection must be used with caution among the elderly because of the high rates of adverse effects http://ow.ly/AmmM30m7bYd

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ABSTRACT Latent tuberculosis infection (LTBI) management is now a critical component of the World Health Organization's End TB Strategy.

In this randomised controlled trial (Chinese Clinical Trial Registry identifier ChiCTR-IOR-15007202), two short-course regimens with rifapentine plus isoniazid (a 3-month once-weekly regimen and a 2-month twice-weekly regimen) were initially designed to be evaluated for rural residents aged 50–69 years with LTBI in China.

Due to the increasingly rapid growth and unexpected high frequency of adverse effects, the treatments were terminated early (after 8 weeks for the once-weekly regimen and after 6 weeks for the twice-weekly regimen). In the modified intention-to-treat analysis on the completed doses, the cumulative rate of active disease during 2 years of follow-up was 1.21% (14 out of 1155) in the untreated controls, 0.78% (10 out of 1284) in the group that received the 8-week once-weekly regimen and 0.46% (six out of 1299) in the group that received the 6-week twice-weekly regimen. The risk of active disease was decreased, with an adjusted hazard ratio of 0.63 (95% CI 0.27–1.43) and 0.41 (95% CI 0.15–1.09) for the treatments, respectively. No significant difference was found in the occurrence of hepatotoxicity (1.02% (13 out of 1279) *versus* 1.17% (15 out of 1279); p=0.704).

The short regimens tested must be used with caution among the elderly because of the high rates of adverse effects. Further work is necessary to test the ultrashort regimens in younger people with LTBI.

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This study is registered at www.chictr.org.cn with identifier ChiCTR-IOR-15007202. The corresponding author can provide, upon request, individual participant data that underlie the results reported in this article (except variables, if any, that may allow identification of patients), after applying necessary measures to guarantee that no individual is identified or identifiable.

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Introduction

Close to a quarter of the global population is latently infected with *Mycobacterium tuberculosis*; millions of active tuberculosis (TB) cases might emerge from this reservoir with a lifetime risk of TB of 5–10% [1–3]. Prevention of disease development through treatment of latent TB infection (LTBI) is now a critical component of the World Health Organization (WHO)'s End TB Strategy [4–6]. China is a high-burden country in terms of both active TB and LTBI, but no national guidelines on LTBI management have yet been developed. Only targeting the high-risk populations recommended by the WHO guidelines, *e.g.* people living with HIV and close household contacts, for LTBI management might not achieve a significant decline in the incidence of TB because these populations contribute only a small minority of active TB cases in China [7, 8]. For example, in 2017, only 1% of incident TB cases were HIV-positive in China compared with 10% in America and Europe and 60% in South Africa [1]. Therefore, in order to reduce the incidence of TB, selecting at-risk populations for LTBI management should adapt to the national epidemiology of TB and other local determinants [5, 6].

Our observational studies reported that half of new infections and three-quarters of active disease occur among individuals aged >50 years in the general population in China [7, 9, 10]. Modelling analysis indicated that preventative therapy in the elderly would be the most effective single intervention to accelerate the decline in the incidence of TB in China if it could be made feasible by managing the relatively high risks of hepatic adverse events [11–14]. Nevertheless, in our view, it is still a theoretical exploration to extend LTBI management to all elderly populations in high-burden countries like China. It is a major challenge to balance the benefits and risks of LTBI treatment in the elderly at the public health level. Targeting subgroups in the elderly at higher risk of developing active disease, such as those with a history of prior TB, would be meaningful and feasible in the current situation. Our previous report proposed that the incidence of TB might decline by 30% in rural communities if effective LTBI intervention is provided for those individuals with prior TB and >50 years old [7]. This accounts for only 3% of the rural population, while it largely improves the cost-efficacy of the targeted intervention at a community level.

In addition, with doubt, short-course regimens with balanced safety are a significant advance in vulnerable populations and in resource-limited areas [15, 16]. Currently, a 3-month once-weekly regimen with rifapentine plus isoniazid (3HP, both with a maximum dose of 900 mg) is the shortest regimen recommended by the WHO [5, 6]. In fact, another 3-month regimen with twice-weekly rifapentine plus isoniazid ($3H_2P_2$, both with a maximum dose of 600 mg) has been practised in China for years [17, 18]. However, it had been not been evaluated by randomised controlled trials (RCTs). No study has yet been conducted to evaluate the performance of short-course regimens for LTBI treatment in elderly populations in China or worldwide.

Our aim was to explore optimised LTBI therapy for at-risk subgroups in the elderly under the conditions in China. Our initial design was to evaluate the safety and protective efficacy of two short-course regimens, 3HP and $2H_2P_2$ (modified from $3H_2P_2$; a 2-month twice-weekly regimen of rifapentine plus isoniazid with a maximum dose of 600 mg for each), for selected rural residents aged 50–69 years by means of an RCT.

Methods

Study regimens

We conducted an open-label, pragmatic RCT with two intervention groups and one untreated control group. Group A (treated with the 3HP regimen): 3 months of once-weekly rifapentine (at a dose up to 900 mg, with incremental adjustment for subjects weighing ⩽50 kg) plus isoniazid (at a dose of 15–25 $mg{\cdot}kg^{-1}$ body weight, rounded up to the nearest 50 mg, with a maximum dose of 900 mg). Group B (treated with the $2H_2P_2$ regimen): 2 months of twice-weekly rifapentine (at a dose of 600 mg, with incremental adjustment for subjects weighing ⩽50 kg) plus isoniazid (at a dose of 15 $mg{\cdot}kg^{-1}$ body weight, rounded up to the nearest 50 mg, with a maximum dose of 600 mg). Group C: untreated controls. Both of the drug regimens were delivered after meals under direct observation.

Details of the study design are provided in the trial protocol (supplementary material). The trial was registered at the Chinese Clinical Trial Registry with identifier ChiCTR-IOR-15007202.

Ethical review

The study protocol was approved by the ethics committees of the Institute of Pathogen Biology, Chinese Academy of Medical Sciences, Beijing, China (approval IPB-2015-5). Written informed consent was obtained from all study participants for baseline LTBI testing and other examinations. Considering the limited educational background of the studied rural elderly, we visited eligible participants again for written informed consent before randomisation to guarantee they were clearly aware of their rights and duties in the study. Untreated controls were settled and permitted for the following considerations: 1) this is the first RCT to evaluate the performance of 3HP in a Chinese population, so no previous data on efficacy and safety was available; and 2) no global or regional guidelines have suggested the elderly as one of the target populations for LTBI management, lacking evidence in benefit–risk analysis for this specific population in worldwide. Proswell Medical Company (Beijing, China) provided independent monitoring during study implementation.

Sample size determination

The study was designed to assess the protective effectiveness of the studied regimens compared with untreated controls. The protective rate in 2 years was assumed to be 70% for the two regimens on the basis of an assumed effectiveness of 70% for isoniazid [19, 20]. Without treatment, the risk of active TB among this study population in 2 years was estimated to be 2%. Thus, assuming 20% treatment discontinuation and/or loss to follow-up for the intervention group and 10% treatment discontinuation and/or loss to follow-up for the control group, we determined that a sample size of 1300 subjects in the intervention group and 1140 subjects in the control group would provide a power of 80% on the basis of an α level of 0.05 and a two-sided test. We assumed that 20% of rural residents aged 50–69 years were interferon-γ release assay (QuantiFERON-TB Gold In-Tube (QFT); Qiagen, Germantown, MD, USA)-positive, and 90% of subjects with LTBI would meet the inclusion and exclusion criteria; therefore, a total of 20 777 rural residents aged 50–69 years needed testing for LTBI to meet the statistical requirements.

Study population and baseline screening

The target population was rural residents aged 50–69 years registered in Zhongmu County, an area with a national average epidemic of TB in China. Baseline screening was conducted between July 29, 2015 and December 6, 2015. In short, for each study participant, trained interviewers collected sociodemographic information by use of a standardised questionnaire. Blood samples were collected for QFT testing and other laboratory tests. QFT testing was performed as recommended by the manufacturer using a cut-off value of $\geqslant 0.35$ IU·mL^{-1} for a positive result. Current active or suspected TB was excluded from asymptomatic participants with positive QFT results by digital chest radiography evaluation. Participants with suspected symptoms and/or abnormal chest radiography findings were transferred to the local Center for Diseases Control and Prevention for diagnosis.

All eligible subjects were required to: 1) be 50–69 years old, 2) be local rural residents who would be able to complete the whole study period, 3) have a positive QFT result and 4) voluntarily sign the informed consent form. Exclusion criteria included: 1) confirmed or suspected current active TB; 2) self-reported or registered prior TB; 3) pregnant or lactating females or females preparing for pregnancy; 4) a history of LTBI prophylactic treatment with rifapentine persistently for >14 days or with isoniazid intermittently for >30 days in the previous 2 years; 5) contraindication for rifapentine or isoniazid; 6) liver dysfunction or impairment (serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN), and/or total bilirubin >1.5×ULN, and/or accompanied by liver impairment symptoms and signs); 7) white blood cell count $<2.0\times10^9$ L^{-1}; 8) positive for hepatitis B virus (HBV) surface antigen and/or antibody to hepatitis C virus (HCV) and/or antibody to HIV; 9) renal insufficiency or degeneration; 10) autoimmune diseases or undergoing treatment with immunosuppressive agents; 11) addicted to drinking or actively using street drugs; 12) without capacity to act independently owing to mental disorders or disability; and 13) other conditions inapplicable for participation in this study judged by the investigator, such as failing to cooperate in the test or complete the whole study.

Formal assessment for treatment eligibility included acquiring a second informed consent before the intervention treatment was ended by November 6, 2015.

Randomisation and intervention implementation

Eligible participants were assigned to study Groups A, B and C according to simple unrestricted randomisation with a sample size ratio of 1:1:0.9 (A:B:C), given a lower loss to follow-up rate in Group C. All participants included in the intervention groups started treatment with the same schedule.

Information on adverse events and side-effects was self-reported by participants at the time of occurrence or collected by researchers at direct observations. Clinical examinations monitoring side-effects were performed once a month or at a frequency determined by the physicians according to the situation during treatment.

Follow-up examinations and end-points

Subjects were followed for 24 months after treatment. All participants were evaluated at 3 months after treatment to monitor long-term side-effects. In addition, study follow-up for active case finding occurred quarterly by TB symptom review through door-to-door or telephone surveys and yearly by chest radiography screening.

The primary study end-points were microbiologically confirmed active pulmonary TB or clinically determined pulmonary TB. Individuals with positive results by sputum smear, culture and/or GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) were confirmed as active TB. Response to empiric TB treatment among participants suspected as having TB but negative to microbiological tests was evaluated for a diagnosis of clinical TB by consensus from a panel of experts consisting of four radiologists, two clinical experts and one laboratory expert. TB diagnosis was made by the expert panel blinded to treatment assignment.

Additional secondary end-points were completion of study therapy, permanent discontinuation of therapy and permanent discontinuation because of an adverse drug reaction, any grade 3 or 4 drug-related toxic effects, or death from any cause. Adverse events and side-effects were graded by investigators using the Common Terminology Criteria for Adverse Events (version 4.0). Two physicians, blinded to treatment allocation, co-determined whether the reported side-effect was study drug related.

Individual treatment termination was determined by the physicians based upon clinical needs. To guarantee the safety of the treated elderly, early termination of the therapy for all participants could be considered but should be approved by the ethics committees. Such early termination was determined by conservative criteria based on existing evidence for the 3HP regimen until October 2015 (supplementary material files S1 and S2): 1) occurrence of high-grade events (grade 3 or 4) >5% and there is still a trend of growth, 2) occurrence of hepatotoxicity (defined by AST/ALT >3×ULN with symptoms or AST/ALT >5×ULN) >1% and there is still a trend of growth, and 3) any other unexpected condition that might damage the risk–benefit balance in the study population as evaluated by the researchers and ethics committees.

Statistical analysis

The frequency of categorical variables in the study participants was compared between groups using the Chi-squared test. The intention-to-treat analysis included all enrolled eligible subjects in each group. The per-protocol population included all eligible enrolled subjects who completed the assigned study regimen (defined as completed ⩾90% doses of therapy). Incidence rates of active TB were assessed at 24 months after the completion of therapy. To identify potential variables related to the risk of side-effects, all variables showing significant relations in the univariate analysis were entered into the unconditional multiple logistic regression analyses, and the associations were then assessed by means of odds ratios and 95% confidence intervals. To identify potential variables related to active disease risk, Cox proportional hazards regression models were fitted to estimate hazard ratios. The time duration for each participant involved in the study was calculated based on the quarterly follow-up records. All variables with $p<0.05$ in univariate models were entered into the multivariate models.

Results

Study participants

As shown in figure 1, a total of 20555 rural residents aged 50–69 years were investigated and 19891 of them completed a physical examination. 4116 participants were identified to be QFT-positive, with a prevalence of 20.69% (4116 out of 19891). During study participant enrolment, 378 QFT-positive individuals were excluded according to the exclusion criteria and 3738 subjects were included for randomisation.

After randomisation, the 3738 eligible participants were classified into three groups: 1284 in Group A (for treatment with the 3HP regimen), 1299 in Group B (for treatment with the $2H_2P_2$ regimen) and 1155 in Group C (untreated controls). The clinical and demographic characteristics of the intention-to-treat population are shown in table 1. Of the 3738 included eligible participants, 2054 (54.95%) were males, 1522 (40.72%) had a current or past history of smoking, 281 (7.52%) had diabetes based on fasting blood glucose >7 $mmol{\cdot}L^{-1}$ and 64 (1.71%) were identified with pulmonary fibrotic lesions by chest radiography.

All of the variables were evenly distributed, except for significantly less pulmonary fibrotic lesions in Group B (1.08%) compared with Group C (2.42%).

Early termination of treatment

Both of the regimens were terminated early due to the unexpected high frequency of side-effects (supplementary files S1 and S2). As approved by the ethic committees, the course of regimen A was modified to 8 weeks (between November 7, 2015 and January 2, 2016) and the course of regimen B was modified to 6 weeks (between November 25, 2015 and January 2, 2016). As shown in table 2, the completion rate of modified regimen A was 85.20% (1094 out of 1284), with 40.53% (77 out of 190) discontinuing treatment due to side-effects. The completion rate of modified regimen B was 78.06% (1014

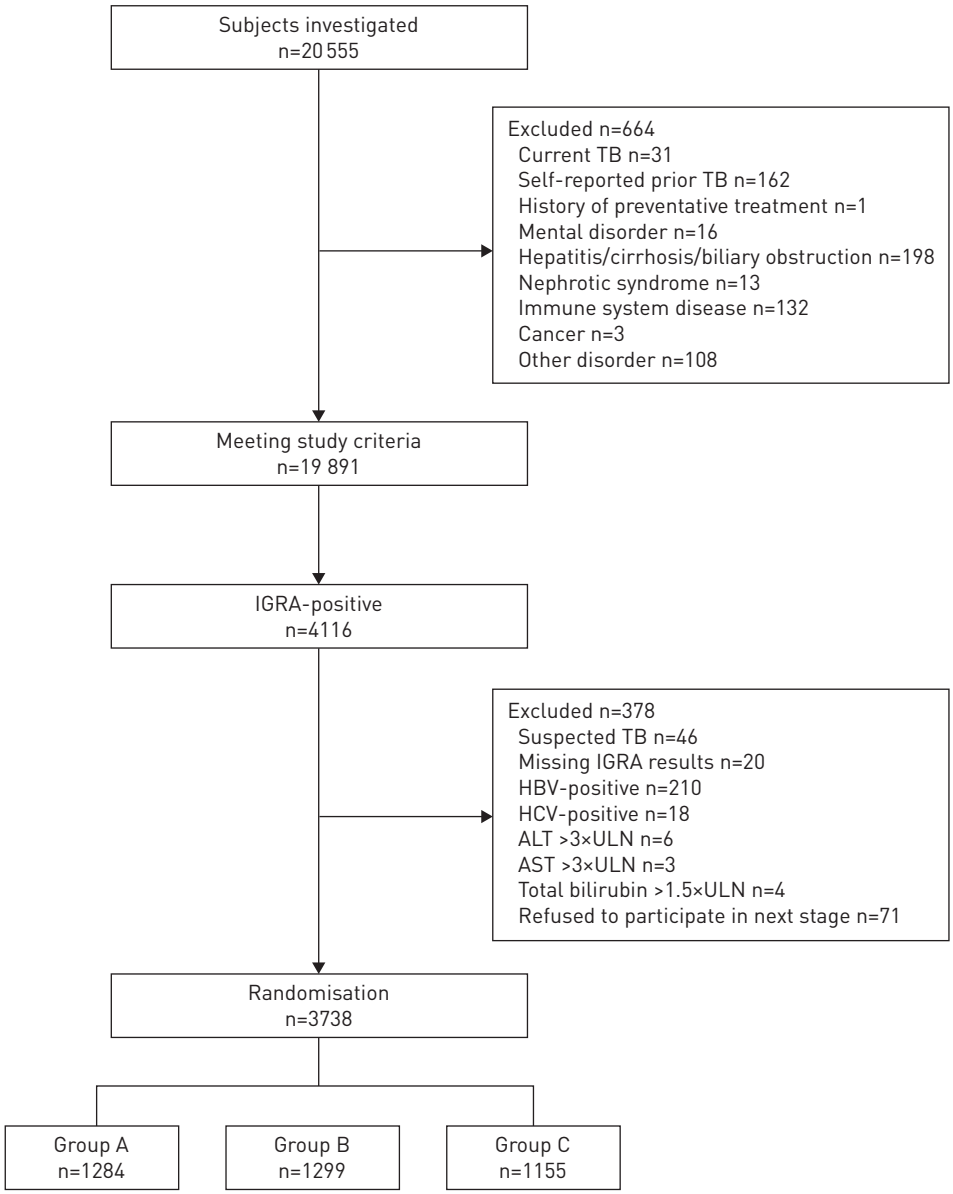

FIGURE 1 Flowchart of study participant enrolment and randomisation. TB: tuberculosis; IGRA: interferon-γ release assay; HBV: hepatitis B virus; HCV: hepatitis C virus; ALT: alanine aminotransferase; ULN: upper limit of normal; AST: aspartate aminotransferase. A total of 20 555 rural residents aged 50–69 years were investigated and 19 891 of them completed a physical examination. 4116 participants were identified to be IGRA (QuantiFERON-TB Gold In-Tube)-positive; 378 of them were excluded according to exclusion criteria and 3738 were included for randomisation. Finally, participants were classified into three groups with a sample size ratio of 1:1:0.9 (A:B:C), given a lower loss to follow-up rate in Group C.

TABLE 1 Characteristics of the study participants included in the intention-to-treat analysis

	Group A[#]	Group B[¶]	Group C[+]	Total
Subjects	1284	1299	1155	3738
Male	703 (54.75)	709 (54.58)	642 (55.58)	2054 (54.95)
Age years				
50–55	329 (25.62)	317 (24.40)	265 (22.94)	911 (24.37)
56–60	332 (25.86)	344 (26.48)	295 (25.54)	971 (25.98)
61–65	347 (27.02)	333 (25.64)	302 (26.15)	982 (26.27)
66–69	276 (21.50)	305 (23.48)	293 (25.37)	874 (23.38)
BMI kg·m^{-2}				
<18.5	37 (2.88)	30 (2.31)	22 (1.90)	89 (2.38)
18.5– <24	523 (40.73)	543 (41.80)	472 (40.87)	1538 (41.14)
24– <28	517 (40.26)	493 (37.95)	459 (39.74)	1469 (39.30)
⩾28	207 (16.12)	233 (17.94)	202 (17.49)	642 (17.17)
Completed primary school	721 (56.20)	734 (56.59)	635 (57.89)	2090 (55.91)
Married	1273 (99.14)	1289 (99.23)	1146 (99.22)	3708 (99.20)
Household per capita income >RMB6000	678 (52.80)	655 (50.42)	607 (52.55)	1940 (51.90)
Ever-smoker	526 (40.97)	534 (41.11)	462 (40.00)	1522 (40.72)
Current alcohol drinker	403 (31.39)	398 (30.64)	342 (29.61)	1143 (30.58)
Pulmonary fibrotic lesions	22 (1.71)	14 (1.08)[§]	28 (2.42)	64 (1.71)
Fasting blood glucose >7 mmol·L^{-1}	92 (7.17)	87 (6.70)	102 (8.83)	281 (7.52)
History of silicosis	31 (2.41)	28 (2.16)	24 (2.08)	83 (2.22)

Data are presented as n or n (%). BMI: body mass index. [#]: intervention Group A completed 8 weeks of once-weekly rifapentine plus isoniazid (both with a maximum dose of 900 mg); [¶]: intervention Group B completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg); [+]: blank controls untreated; [§]: p-value for Chi-squared test <0.05 between Group B and Group C.

out of 1299), with 28.77% (82 out of 285) discontinuing treatment due to side-effects. More detailed information on therapy completion is given in supplementary material file S3.

Protective effect of the modified regimens

In total, 30 incident cases of active pulmonary TB were diagnosed during the follow-up (supplementary material file S4). Supplementary material file S5 shows the Kaplan–Meier curve of time to active TB by study arm. Two cases were confirmed microbiologically, while 28 cases were diagnosed clinically based on their responses to anti-TB treatment. In the intention-to-treat analysis (table 3), the cumulative incidence

TABLE 2 Completion of the modified regimens and attribution for treatment discontinuation

Modified regimen A[#]	1284
7–8 doses (completed)[¶]	1094 (85.20)
<7 doses (uncompleted)	190 (14.80)
Drug side-effects[+]	77 (40.53)
Refusal to continue	50 (26.32)
Unreachable	33 (17.37)
Other reasons	30 (15.79)
Modified regimen B[§]	1299
11–12 doses (completed)[¶]	1014 (78.06)
<11 doses (uncompleted)	285 (21.94)
Drug side-effects[+]	82 (28.77)
Refusal to continue	98 (34.39)
Unreachable	51 (17.89)
Other reasons	54 (18.95)

Data are presented as n or n (%). [#]: intervention Group A completed 8 weeks of once-weekly rifapentine plus isoniazid (both with a maximum dose of 900 mg); [¶]: defined as completed ⩾90% doses of therapy, *i.e.* completed ⩾7 doses for modified regimen A and ⩾11 doses for modified regimen B; [+]: side-effects were identified and graded by physicians blinded to treatment allocation according to the Common Terminology Criteria for Adverse Events (version 4.0); [§]: intervention Group B completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg).

TABLE 3 Incidence of active tuberculosis in the study groups

	Group A treated with modified regimen A[#]	Group B treated with modified regimen B[¶]	Group C untreated
Intention-to-treat analysis			
Subjects n	1284	1299	1155
Person-years n	2419	2471	2057
Incident cases n	10	6	14
Cumulative incidence (95% CI) %	0.78 (0.30–1.26)	0.46 (0.17–1.00)	1.21 (0.58–1.84)
Protective rate[+] %	35.54	61.98	
Incidence rate per 100 person-years (95% CI)	0.41 (0.21–0.74)	0.24 (0.14–0.51)	0.68 (0.38–1.12)
Protective rate[§] %	39.71	64.71	
Adjusted hazard ratio (95% CI)[f]	0.63 (0.27–1.44)	0.41 (0.15–1.08)	Reference
Per-protocol analysis			
Subjects n	1093	1015	1155
Person-years n	2087	1951	2057
Incident cases n	9	4	14
Cumulative incidence (95% CI) %	0.82 (0.29–1.36)	0.39 (0.10–0.78)	1.21 (0.58–1.84)
Protective rate[+] %	32.23	67.77	
Incidence rate per 100 person-years (95% CI)	0.43 (0.21–0.79)	0.21 (0.07–0.49)	0.68 (0.38–1.12)
Protective rate[§] %	36.76	69.12	
Adjusted hazard ratio (95% CI)[f]	0.64 (0.27–1.50)	0.34 (0.11–1.06)	Reference

[#]: 8 weeks of once-weekly rifapentine (at a maximum dose of 900 mg) plus isoniazid (at a maximum dose of 900 mg); [¶]: 6 weeks of twice-weekly rifapentine (at a maximum dose of 600 mg) plus isoniazid (at a maximum dose of 600 mg); [+]: calculating protective rate by using cumulative incidence; [§]: calculating protective rate by using incidence rate per 100 person-years; [f]: adjusted for age, sex, body mass index, current alcohol drinking and presence of pulmonary fibrotic lesions.

of active TB was 1.21% (95% CI 0.58–1.84%) in the untreated control Group C, 0.78% (95% CI 0.30–1.26%) in the modified Group A and 0.46% (95% CI 0.17–1.00%) in the modified Group B. Compared with the untreated controls, the risk of active disease was decreased among individuals treated with modified regimen A (adjusted HR 0.63, 95% CI 0.27–1.43) and modified regimen B (adjusted HR 0.41, 95% CI 0.15–1.09). In the per-protocol analysis, the protection rates were 36.76% for modified regimen A and 69.12% for modified regimen B.

Among a total of 475 individuals (190 in Group A and 285 in Group B) who did not complete the modified regimens, three of them (one in Group A and two in Group B) developed active TB during the 2 years of follow-up, with a cumulative incidence of 0.63%. Among 320 individuals with LTBI but excluded before randomisation, five of them developed active TB during the 2 years of follow-up, with a cumulative incidence of 1.56%.

Adverse events

A total of 29 deaths occurred during the study period in the three groups. No significant difference in mortality was observed between the groups (p=0.245) and none of the deaths were attributed to LTBI treatment (supplementary material file S6). As shown in table 4, there was no significant difference between the intervention groups in the occurrence of any adverse or serious adverse events. For both groups, the occurrence of symptomatic liver injury and abnormal liver function (ALT/AST) was remarkably increased after 4 weeks of treatment (supplementary material file S7). The proportion of subjects with hepatotoxicity was similar between the two treatment groups (1.02% in Group A *versus* 1.17% in Group B; p=0.704). Occurrences of other study drug-related side-effects are given in detail in supplementary material files S8 and S9. In short, modified regimen A showed significantly higher proportions of gastrointestinal reactions (8.60%; p=0.006) and influenza-like symptoms (3.60%; p=0.046) compared with modified regimen B (5.16% and 2.27%, respectively). A much higher frequency of hypersensitivity or allergy was observed for modified regimen B (5.08%) than modified regimen A (3.36%; p=0.031). No significant difference in hospitalisation due to side-effects was found between the two regimens (supplementary material file S10).

All side-effects recovered after terminating treatment or giving clinical management. Monitoring the long-term effects of preventative therapies, a total of seven subjects were identified with elevated ALT/AST >3×ULN, but none of them had >5×ULN and no renal dysfunction was identified.

TABLE 4 Characteristics of the participants with adverse events and study drug side-effects

	Group A[#]	Group B[¶]	p-value for Chi-squared test
Subjects	1279	1279	
Adverse events[+]			
Subjects with any adverse event	295 (23.06)	277 (21.66)	0.393
Death	1 (0.08)	0 (0)	0.999
Occurrence of serious adverse events			
Yes	18 (1.41)	17 (1.33)	0.865
No	277 (21.66)	260 (20.33)	0.409
Frequency per person			
1 event	265 (20.72)	248 (19.39)	0.401
>1 event	30 (2.35)	29 (2.27)	0.895
Attributed to drug			
Yes	244 (19.08)	219 (17.12)	0.199
No	51 (3.99)	58 (4.53)	0.493
Classified by event severity grade			
Grade 1	212 (16.58)	182 (14.23)	0.100
Grade 2	51 (3.99)	63 (4.93)	0.250
Grade 3	30 (2.35)	32 (2.50)	0.797
Grade 4/5	3 (0.23)	1 (0.08)	0.625
Side-effects[+]			
Subjects with any side-effect	244 (19.08)	219 (17.12)	0.199
Specific side-effect			
Gastrointestinal reaction	110 (8.60)	66 (5.16)	0.006
Hypersensitivity or allergy	43 (3.36)	65 (5.08)	0.031
Influenza-like symptoms[§]	46 (3.60)	29 (2.27)	0.046
Hepatotoxicity[f]	13 (1.02)	15 (1.17)	0.704
Other drug reactions	116 (9.07)	111 (8.68)	0.728
Categories occurring per person			
1	177 (13.84)	163 (12.74)	0.415
2	53 (4.14)	45 (3.52)	0.410
⩾3	14 (1.09)	11 (0.86)	0.547
Hospitalisation due to side-effects	4 (0.31)	6 (0.47)	0.753

Data are presented as n or n (%), unless otherwise stated. ULN: upper limit of normal. [#]: completed 8 weeks of once-weekly rifapentine plus isoniazid (both with a maximum dose of 900 mg); [¶]: completed 6 weeks of twice-weekly rifapentine plus isoniazid (both with a maximum dose of 600 mg); [+]: adverse events and side-effects were identified and graded by physicians using the Common Terminology Criteria for Adverse Events (version 4.0); [§]: influenza-like symptoms include chills, hyperpyrexia, headache, asthma, dyspnoea, generalised soreness, arthralgia, *etc.*; [f]: elevations of serum alanine aminotransferase and/or aspartate aminotransferase >3×ULN with accompanying symptoms or >5×ULN without symptoms.

Risk factors

The multiple logistic regression analysis (table 5) indicated that male sex was associated with a lower risk of side-effects than female sex (adjusted OR 0.73, 95% CI 0.53–0.99). The risk of side-effects decreased with an increase of body mass index (BMI) (adjusted OR 0.94, 95% CI 0.91–0.97), with the highest proportion of side-effects (23.88%) observed among those with BMI <18.5 $kg{\cdot}m^{-2}$ and the lowest (15.27%) among those with BMI ⩾28 $kg{\cdot}m^{-2}$. The risk of side-effects increased among the participants taking concomitant drugs (adjusted OR 2.12, 95% CI 1.65–2.71).

As shown in supplementary material file S11, the incidence of active TB increased along with age in a dose–response relationship. Participants with baseline BMI <18.5 $kg{\cdot}m^{-2}$ had a much higher hazard of developing active disease (adjusted HR 3.15, 95% CI 1.01–9.77). Current alcohol drinking was found to be related to declining risk of disease. After excluding self-reported or registered TB patients, individuals with pulmonary fibrotic lesions identified by chest radiography were at a much higher risk of developing active TB compared with those with normal chest radiography (adjusted HR 6.77, 95% CI 2.29–19.97).

Discussion

This is the first pragmatic RCT from China addressing LTBI treatment among individuals aged >50 years. Neither 3HP (3 months of once-weekly rifapentine plus isoniazid, both with a maximum dose of 900 mg) nor $2H_2P_2$ (2 months of twice-weekly rifapentine plus isoniazid, both with a maximum dose of 600 mg)

TABLE 5 Risk factors associated with the occurrence of side-effects[#]

	Proportion with side-effects[¶] n/N (%)	p-value for Chi-squared test	Adjusted OR (95% CI)
Age years			
⩽60	219/1273 (17.20)	0.039	Reference
>60	244/1193 (20.45)		1.20 (0.97–1.47)
Sex			
Female	238/1121 (21.23)	0.004	Reference
Male	225/1345 (16.73)		0.73 (0.53–0.99)
BMI kg·m^{-2}			
<18.5	16/67 (23.88)	0.059	
18.5– <24	211/1019 (20.72)		
24– <28	172/961 (17.90)		
⩾28	64/419 (15.27)		
p_{trend}		0.014	0.94 (0.91–0.97)
Ever-smoker			
No	293/1457 (20.11)	0.041	Reference
Yes	170/1007 (16.85)		0.99 (0.71–1.38)
Current alcohol drinking			
No	327/1701 (19.22)	0.395	
Yes	136/765 (17.78)		
Pulmonary fibrotic lesions			
No	451/2416 (18.67)	0.068	
Yes	11/36 (30.56)		
Fasting blood glucose mmol·L^{-1}			
⩽7	434/2295 (18.91)	0.528	
>7	29/171 (16.96)		
History of silicosis			
No	449/2409 (18.64)	0.257	
Yes	14/57 (24.56)		
Concomitant with other drugs			
No	346/2066 (16.75)	<0.001	Reference
Yes	117/400 (29.25)		2.12 (1.65–2.71)

BMI: body mass index. [#]: side-effects were identified and graded by physicians using the Common Terminology Criteria for Adverse Events (version 4.0); [¶]: the events in the two intervention groups were pooled for this analysis.

was completed as scheduled due to the increasingly rapid growth and unexpected high frequency of drug-related side-effects. Nevertheless, in the 2 years of follow-up for the modified regimens, the 6-week twice-weekly regimen still showed a protective efficacy >60%.

Treatment of LTBI can effectively reduce the risk of active TB development with an efficacy ranging from 60% to 90% and has long been considered an essential component of TB control in low-incidence countries [21]. Since 2015, the WHO has called for the global goal to end the TB epidemic [4] by strengthening and expanding preventative treatment to high-risk groups as a means to accelerate the decline in the incidence of TB [5, 6]. Preventative therapy in the elderly with LTBI was suggested to be one effective tool to accelerate the decline in the incidence of TB in China [12, 13]. However, data on safety and efficacy of LTBI therapies using domestic drugs in the elderly Chinese are lacking. Our results provide direct evidence that the risks of 3HP are considerable among the elderly. The hepatotoxicity rate of 1% is 2.5 times the rate observed in the landmark trial on 3HP [19] and the rate of hospitalisation was 0.3%, 3 times higher than reported [22]. It might be attributed to a lower tolerance to anti-TB drugs in the elderly [15, 16]. Recently, more results of the application of 3HP in various populations have been reported [23–25]. Rates of hepatotoxicity among patients taking 3HP were lower than comparators in all RCTs. However, it is still difficult to extract safety data for the elderly from these heterogeneous studies [26]. In a small RCT from Taiwan, 1.5% (two out of 132) of participants undergoing 3HP treatment reported clinically relevant hepatotoxicity [27]. This was the first safety data for 3HP from a Chinese population, but it was achieved from a young population with a mean age of 32 years. In addition, compared with foreign drugs, the varied performance of domestic drugs might be another possible explanation. Unfortunately, no foreign rifapentine and isoniazid are currently approved in China. The fast-growing occurrence of self-reported symptoms and/or laboratory-confirmed hepatotoxicity

(supplementary material file S7) raises concerns for even higher rates if therapy had been allowed to continue [28, 29]. Our initially designed $2H_2P_2$ regimen was adapted from the 3-month twice-weekly rifapentine plus isoniazid regimen ($3H_2P_2$, both with a maximum dose of 600 mg) [17, 18]. A non-RCT has been conducted for tuberculin skin test-positive college students using $3H_2P_2$ (1948 treated and 1765 untreated); the occurrence of liver dysfunction (ALT/AST higher than normal level) was reported to be 2% and the protective rate was observed to be 75% during 4 years of follow-up [17]. Compared with 3HP, $3H_2P_2$ was determined mainly based on the following two points. 1) It was reported that the genetic background, such as drug-metabolising enzyme gene polymorphisms, may contribute to various risks of anti-TB drug-induced liver injury (*e.g.* the cytochrome P450 2E1 genotype *CYP2E1* *1A/*1A has been found to be associated with lower tolerance to anti-TB drugs in East Asians [30]). 2) Asians have been reported to carry a higher frequency of rapid acetylator genotypes of *N*-acetyltransferase 2 (~50%) than Caucasians (~5%). *N*-acetyltransferase 2 is the major drug-metabolising enzyme of isoniazid and people are identified as rapid or slow acetylators according to its activity. Rapid acetylators are prone to treatment failure, probably due to insufficient exposure to isoniazid [31]. Thus, reduced single dosage and increased frequency were adopted in $3H_2P_2$. In our trial, $3H_2P_2$ was shortened to $2H_2P_2$ at initial study design to improve the tolerance of the elderly.

Efficacy evaluations were implemented to the early terminated regimens, which were modified to a 8-week once-weekly regimen and a 6-week twice-weekly regimen, respectively. This is the first trial to provide safety and efficacy data for such short-course regimens based on rifapentine and isoniazid in the elderly from the general population. It is noteworthy that the 6-week regimen showed a protective efficacy >60%, which was twice the efficacy observed for the 8-week once-weekly regimen. This provides a positive outlook for the development of a shorter treatment regimen than is currently recommended for the elderly with LTBI. Although the pooled dosages of the two regimens were equal (7200 mg) and the risks of side-effects were also similar, the twice-weekly regimen showed better efficacy and proved to be more suitable for the elderly Chinese population. Research on the pharmacokinetics of the drugs in special populations is warranted to better define an innovative treatment regimen with optimal doses and dosing schedules.

Although the 6-week twice-weekly regimen showed better protection, the completion rate was lower than for the 8-week regimen (8 doses) (78.06% *versus* 85.20%; $p<0.001$). The most frequent reason for early termination was refusal to continue (34.39%) rather than side-effects (28.77%) in the 6-week regimen. The total number of doses and the frequency of drug delivery seemed to significantly influence LTBI therapy adherence. In March 2018, Richard Chaisson (Johns Hopkins University, Baltimore, MD, USA) shared results of the ACTG 5279 phase 3 trial (ClinicalTrials.gov identifier NCT01404312) at the 2018 Conference on Retroviruses and Opportunistic Infections (Boston, MA, USA). This trial found that the 1-month rifapentine plus isoniazid regimen was noninferior to 9-month isoniazid in HIV-infected adults and adolescents. More recently, an open-label trial conducted in nine countries reported the 4-month regimen of rifampin was noninferior to 9-month isoniazid for the prevention of active TB [32]. Such short-course or ultrashort-course therapies showed fewer adverse events and higher treatment completion, and were suggested to be important tools to control the TB epidemic.

We did not find a relationship between the baseline elevations of AST/ALT and the occurrence of hepatotoxicity during the treatments. Nearly all of the participants (47 out of 48) had asymptomatic marked elevations in liver function tests (AST/AST >3×ULN). None of the patients with hepatotoxicity were identified in the first month of treatment and severe liver injuries occurred quickly later in the course of therapy (supplementary material file S4). Therefore, baseline and liver function monitoring is needed throughout LTBI treatment among the elderly, especially those with drinking habits.

Individuals with underlying liver disease from HBV/HCV infection and viral hepatitis were excluded from our study and cannot explain the high rate of drug-induced hepatotoxicity [19, 33]. However, HBV infection is still common in China, especially in the elderly [34], and may increase the rates of hepatotoxicity. Therefore, future studies are needed to address this viral comorbidity in high-burden regions.

Our study has several other limitations. First, although different from the Peto–Haybittle rule for stopping trials early for lack of evidence of benefit [35, 36], our study terminated the designed treatment early due to side-effects and the precision of the outcome estimates for the modified regimen based on the original study settings might also be biased [37, 38]. For example, for the 6-week twice-weekly regimen, our study only has a power of 54% to detect a protective rate of 62% at the significance level of 0.05 (95% confidence level). Therefore, further RCTs are warranted to systematically evaluate the efficacy of this ultrashort-course regimen and our study provided essential data for the study design of such trials. Second, the 2-year follow-up limits the assessment of long-term protection of the study regimens. Our

previous study found the elderly in rural China had a higher risk of TB infection acquisition [10], which might shorten the protection period of the treatment compared with settings with a lower risk of TB transmission. This information would be very important for strategic policy development and, hence, we will maintain the study cohorts for longer-term evaluation. Third, study participants with pulmonary fibrotic lesions were not evenly distributed between the groups, which can influence the estimation of protection because prior TB is a risk factor for disease development among individuals with LTBI [7]. However, after excluding participants with pulmonary fibrotic lesions, the protective efficacy of the 6-week regimen was still 47.19% (supplementary material file S12). Fourth, we observed fewer active TB cases than expected. This might be partly explained by the strict exclusion criteria by which some individuals with risk factors for disease were excluded, thereby potentially creating a bias toward higher protection rates found in the study. Additionally, strict exclusion criteria limited the applicability of our findings in the excluded individuals. Fifth, most of the incident cases (28 out of 30) were clinically diagnosed by active case finding in this study. However, we used an expert team to determine clinical diagnosis, blinded to group assignment, based on responses to diagnostic anti-TB treatment. This guaranteed the objectivity and traceability of diagnosis, and minimised the bias caused by misclassification. Nevertheless, there is a need to increase the positive detection rate of microbiological tests, for one, by improving sputum quality.

In conclusion, while the short LTBI regimens tested had fairly high efficacy and look promising, high rates of adverse effects led to early termination of both arms. Thus, these regimens must be used with caution among the elderly. The 6-week twice-weekly rifapentine plus isoniazid regimen showed a protective efficacy >60% in our study population. Such innovative regimens with ultrashort courses and optimised use of drugs are urgently needed, especially in high-burden countries, for the global plan of the End TB Strategy. Our findings indicate ultrashort LTBI treatment for at-risk subgroups might be feasible and practicable, but needs further tests in varied populations.

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