

Impacts of 12-dose regimen for latent tuberculosis infection

Treatment completion rate and cost-effectiveness in Taiwan

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Abstract

Treatment of latent tuberculosis infection (LTBI) is essential for eradicating tuberculosis (TB). Moreover, the patient adherence is crucial in determining the effectiveness of TB control. Isoniazid given by DOTS daily for 9 months (9H) is the standard treatment for LTBI in Taiwan. However, the completion rate is low due to the long treatment period and its side effects. The combined regimen using a high dose of rifapentine/isoniazid once weekly for 12 weeks (3HP) has been used as an alternative treatment option for LTBI in the United States. This may result in a higher completion rate. In this pilot study, patient adherence and cost of these 2 treatment regimens were investigated. Thus, we aimed to assess the treatment completion rate and costs of 3HP and compare to those with 9H.

Data from 691 cases of LTBI treatments including 590 cases using the conventional regimen and 101 cases with rifapentine/isoniazid were collected. The cost was the sum of the cost of treatment with Isoniazid for 9 months or with rifapentin/Isoniazid for 3 months of all contacts. The effectiveness was the cost of cases of tuberculosis avoided.

In this study, the treatment completion rate for patients prescribed with the 3 months rifapentine/isoniazid regimen (97.03%) was higher than those given the conventional 9-month isoniazid regimen (87.29%) ($P < 0.001$). The cost of 3HP and 9H was US\$261.24 and US\$717.3, respectively. The cost-effectiveness ratio with isoniazid for 9 months was US\$ 15392/avoided 1 case of tuberculosis and US\$ 5225/avoided 1 case of tuberculosis with 3HP. In addition, when compared with the conventional regimen, there were fewer patients discontinued with rifapentine/isoniazid regimen due to undesirable side effects.

This was the first study to compare the 2 treatment regimens in Taiwan, and it showed that a short-term high-dosage rifapentine/isoniazid treatment regimen reduced costs and resulted in higher treatment completion than the standard LTBI isoniazid treatment.

Abbreviations: 3HP = 3-month rifapentine/isoniazid regimen, 9H = 9-month isoniazid regimen, DOTS = direct observation of treatment, FDA = Food and Drug Administration, LTBI = latent tuberculosis infection, TB = tuberculosis.

Keywords: cost-effectiveness, isoniazid, latent tuberculosis infection treatment, rifapentine

1. Introduction

Tuberculosis (TB) is well known as an airborne infectious disease that is preventable and curable. People who are recently in contact with active TB patient are more likely to have latent tuberculosis infection (LTBI).^[1] The *Mycobacterium tuberculosis* bacilli can remain dormant in the host body for a long period. In

general, people with LTBI usually remain asymptomatic, with only 5% to 10% of cases progress to overt TB disease. Moreover, the risk of LTBI progressing to active TB is the highest risk during the first 6 to 18 months of infection.^[2] During the dormant period, few live *M. tuberculosis* bacilli are present in the host body. Thus, administering drugs to treat LTBI during this period can effectively minimize the risk of subsequent disease development.^[3] Therefore, treating LTBI is a crucial strategy in eradicating TB.

Isoniazid is the main drug for treating LTBI, and it is the only LTBI treatment drug approved by the United States Food and Drug Administration (FDA). After continually taking this prophylactic drug for 9 months, people with LTBI can reduce the likelihood of disease development by 60% to 90%; hence, Isoniazid is an economically viable prophylactic drug.^[4] However, asymptomatic patients who are prescribed Isoniazid tend to have low adherence due to the extensive treatment period and undesirable side effects. Consequently, patients discontinue taking the drug without the consent of clinicians, resulting in medical problems. Therefore, how to effectively administer prophylaxis in a manner that is convenient for people is a concern among medical personnel and studies in this area are ongoing.^[5-8] To ensure adherence to treatment by tuberculosis patients, the direct observation of treatment (DOTS) by a trained supervisor is recommended.

In a recent study, the US CDC has approved treating LTBI by administering a high dosage of combined isoniazid (900 mg) and

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rifapentine (900 mg) once a week for 12 weeks under Directly Observed Treatment, Short Course (DOTS). It can effectively prevent TB and increases patient adherence to treatment.^[9] Researchers from the United States, United Kingdom, and Canada have successively compared the LTBI treatment regimens in terms of economic influence, drug efficacy, immunity duration, and side effects.^[10–12] In Taiwan, patients undergoing TB treatment must take their medications under DOTS.^[13] The need of taking daily TB prophylactic drug under DOTS for 9 months and the potential side effects makes the new regimen look attractive to be implemented in Taiwan. No studies related to the high rifapentine/isoniazid regimen have been conducted in Taiwan, thus this study aims to investigate the effects, costs, and adherence of the 9-month isoniazid regimen (9H) and the 3-month rifapentine/isoniazid regimen (3HP) and compare the differences between the 2 treatments.

2. Methods

2.1. Study population

The active tuberculosis patients referred to the Changhua hospital and had been diagnosed with the need to undertake LTBI treatment were enrolled in the study group, from February to July 2014. Participation criteria were: recent contact with patients who have newly developed TB disease and are not resistant to isoniazid or rifampin. Positive tuberculin skin test result (PPD-RT23 + Tween80 2 TU/0.1 mL Mantoux) with an in duration ≥ 10 mm within 72 hours of undergoing a skin test, or purified protein derivative (PPD) < 10 mm, but measured ≥ 10 mm after 3 months. No clinical TB symptoms, such as coughing, fever, and weight loss. A chest X-ray image presents no sign of disease development or bacteriological evidence (e.g., negative sputum culture). The exclusion criteria were: pregnant women or women who plan to be pregnant. Children younger than 12 years of age. HIV patients who are undergoing antiretroviral therapy. Abnormal liver and kidney function indices, and cirrhosis or uremia diagnosed by a hepatobiliary, gastroenterology, or liver specialist. Frequent contact with patients resistant to isoniazid or rifapentine. Consent forms were given and signed by participants following a full explanation of the importance of LTBI treatment, the treatment course, and potential side effects of the treatment.

In the study group, 12-dose combined regimen of weekly rifapentine (900 mg) plus isoniazid (900 mg) was administered via DOTS. The control group (9H group) comprised TB contacts who were required to receive LTBI treatment after being referred for assessment by the Changhua County Public Health Bureau. The treatment drug was administered once daily for 270 doses (9 months) and was also administered via DOTS. We estimated the direct costs (medications and visits) of 3HP and 9H in contacts. The risk of developing TB of all contacts with LTBI without treatment during the 5 years following the diagnosis of LTBI was estimated according to the method of Vynnycky and Fine.^[14] Thus, the total cost was assessed according to the number of cases of TB avoided as cost-effectiveness.^[15,16] This study was approved by the Institutional Review Board of Chung-Shan Medical University Hospital (CSMUH No: CS12161), and informed written consent to participate in the study was obtained from each participant.

2.2. Data collection

Basic demographic data (such as sex, age, medical history) of the participants were collected and the relationships between the participants and the index cases were investigated. Each month,

the participants underwent a follow-up examination to monitor and record any medication side effects, symptoms as well as their severity. Results of the examination were compared to determine the differences between the 2 treatment groups. Blood samples were collected before administrate the drug (baseline), 1 month after the drug treatment and at the completion of treatment to monitor the liver function of the participants. The results were also compared to determine the different effects on the liver function. While administering the drug, participants who experienced side effects underwent a blood test immediately. Asymptomatic participants with an aminotransferase (AST) level equal to or higher than 5 times the normal level were required to discontinue any medication. Symptomatic participants with an AST level equal to or higher than 3 times the normal level were also required to discontinue their medication. Patients with a baseline liver function exceeding the upper limit of normal, patients with liver disease, patients who were HIV-positive, or alcoholic (high-risk groups for hepatitis) were carefully monitored and underwent monthly liver function tests.

2.3. Statistical analysis

All continuous variables were expressed as the median and range, and the number (n) was expressed as percentages for categorical variables. The χ^2 test and Fisher exact test were used to analyze the difference in medication adherence, types, and severity of side effects from the treatment. Statistical analyses were conducted using SPSS 15.0 statistical software (SPSS, Chicago, IL). Statistical significance was defined as $P < 0.05$ in a 2-tailed test.

3. Results

Among the 104 contacts who provided informed consent to participate in the study, 1 participant was excluded due to the potential interaction of the concurrent medications, and 2 were excluded and their medication was discontinued due to the exclusion of the index cases. The final research sample comprised 44 men and 57 women (mean age, 34.94 years; age range, 13–75 years). Sixteen participants had other chronic diseases, including diabetes, heart disease, and hypertension (Table 1). The participants underwent monthly follow-up examinations, during

Table 1
Characteristics of the 3-month rifapentine/isoniazid regimen (3HP) population and 9-month isoniazid regimen (9H).

Variable	3HP (n=101)	%	9H (n=590)	%
Age (mean) [range]	34.94		34.49	
Sex				
Male	44	43.56%	312	52.88%
Female	57	56.44%	278	47.11%
Comorbidity				
Hypertension	10	9.90%	61	10.33%
Diabetes mellitus	4	3.96 %	21	3.55%
Heart disease	2	1.98%	19	3.22%
Anemia	1	0.99%	3	0.50%
Asthma	1	0.99%	1	0.16%
Favism	1	0.99%	0	0%
Gout	1	0.99%	6	1.01%
Hepatitis	1	0.99%	10	1.69%
Thyroid dysfunction	1	0.99%	2	0.33%

3HP=3-month rifapentine/isoniazid regimen, 9H=9-month isoniazid regimen.

Table 2

The laboratory data of 3HP population.

Variable	Before treatment Median (range)	After treatment (1 months) Median (range)	After treatment (3 months) Median (range)
WBC (mm ³)	7900 (4100–14,000)	6850 (3700–11,100)	7100 (3600–13,800)
Hb (g/dL)	13.7 (7.9–17.1)	13.5 (9.0–16.5)	13.7 (8.7–16.5)
Platelet (10 ³ /μL)	238.5 (149–406)	241.5 (134–390)	219.5 (149–339)
Total bilirubin (mg/dL)	0.68 (0.26–2.09)	0.635 (0.16–1.68)	0.71 (0.29–1.97)
GOT (IU/L)	20.00 (12.00–51.00)	21.00 (6.00–68.00)	20.00 (14.00–63.00)
GPT (IU/L)	19.00 (7.00–85.00)	18.00 (9.00–76.00)	18.00 (6.00–151.00)

Table 3

Treatment results of the 9H and 3HP regimen.

	Control group (9H) (n=590)		Study group (3HP) (n=101)		P value
	No.	%	No.	%	
Treatment results					
Complete	515	87.29%	98	97.03%	<0.001
Incomplete	75	12.71%	3	2.97%	
Reason for incomplete					
Side effect	28	4.75%	3	2.97%	<0.001
Refuse	44	7.46%	0	0.00%	
Died during treatment	1	0.17%	0	0.00%	
Develop into active TB	2	0.34%	0	0.00%	

which they were prescribed for 4 doses of medication and requested to describe any side effect they experienced. Their blood biochemistry values were examined before drug administration, 1 month after drug administration and again after completing the treatment (Table 2). Data from 101 contacts was collected; however, 3 of them discontinued their medication because of side effects. The remaining 98 participants completed the 3-month treatment. Moreover, in the control group, a total of 590 contacts received the 9-month isoniazid treatment (mean age, 34.49 years; age range, 0–88 years), 515 of whom completed the treatment (Table 3). Regarding the remaining 75 contacts who discontinued the treatment in the control group, the main reasons for discontinuing the medication were the extensive treatment period and the severity of the side effects from taking the medication. The difference in the completion rate between the control group (515/590: 87.29%) and experimental group (98/101: 97.03%) was statistically significant ($P < 0.001$), indicating that patients who were administered the short-term high-dosage rifapentine and isoniazid regimen had a high treatment completion rate. In addition, the discontinuation rate was lower in the experimental group (2.97%, 3/101 cases) than in the control group (4.75%, 28/590 cases) (Table 3).

During the follow-up examinations in the experimental group, elevation of GOT is noted in only 2 cases (2/101 = 1.98%) after the treatment. GOT level of these 2 cases was heightened from 17 IU/L and 16 IU/L to 68 IU/L and 51 IU/L, respectively, while this phenomenon was not observed in the rest of patients. In addition, although not considered significant clinically, a noticeable decrease in averaged WBC count, from 7900 (median) before the treatment to 6850 after the treatment, was seen in our study (Table 2). Moreover, 37 participants reported experiencing uncomfortable side effects, including fever, headache, skin itchiness, and vomiting (Table 4). Furthermore, the side effects of the 3 participants discontinued their medications was listed in Table 5. These 3 patients who discontinued their medication presented a fever higher than 38.5°C and Grade 2 or 3 toxicity. However, in the control group, 28 participants discontinued their

medications due to the side effects (Table 5). The uncomfortable side effects included fatigue (21 cases), headache (3 cases), skin rashes (2 cases), diarrhea (1 case), and chest distress (1 case). Furthermore, elevation of GOT/GPT was noted in 21 cases with fatigue event (21/590 = 3.56%).

Regarding the cost of treatment, according to Taiwanese Labor Law, minimum hourly wages is US\$3.5 per hour and normally DOTS spend an hour for 1 patient approximately. Thus, the medication and labor fee of the 3HP treatment program were approximately US\$219.24 and US\$42.00 respectively (Table 6). On the other hand, the medication and manual costs for the 9H group were approximately US\$24.3 and US\$693.00, respectively. The 9H program was found to be 2.75 times more expensive. Furthermore, the cost-effectiveness ratio with isoniazid for 9 months was US\$ 15392/avoided 1 case of tuberculosis and US\$ 5225/avoided 1 case of tuberculosis with 3HP (Table 7). Therefore, 3HP was dominant in the sensitivity analysis. Therefore, the 3HP treatment was substantially cheaper than 9H.

Table 4

The side effects of the 3-month rifapentine/isoniazid regimen (3HP) population.

(n=44)	Severity of adverse event (no.)		
	Grade 1	Grade 2	Grade 3
Fatigue	9		
Headache	6		
Local reaction	5		
Mood	4		
Allergic reaction	2		
Fever	4	2	2
Vomiting	3	1	2
Diarrhea	1		
Cardiac rhythm		1	
Stomatitis		1	
Malaise	1		

Table 5**Side effects and severity (WHO Toxicity Grading) caused discontinue medication in 9H and 3HP groups.**

9H population (n=28)	Severity of adverse event (no.)			
	Grade 1	Grade 2	Grade 3	Grade 4
GOT/GPT	4	10	1	6
Headache		3		
Chest distress		1		
Diarrhea		1		
Skin rashes		2		

3HP population (n=3)	Severity of adverse event (no.)			
	Grade 1	Grade 2	Grade 3	Grade 4
Fever	1	1	1	
Vomiting			1	
Allergic reaction	1			

Table 6**The medication and labor costs of 3HP and 9H regimens.**

		3HP			9H		
		n	n (once a week)	Cost/patients	n	n (day)	Cost/patients
Medication costs							
Isoniazid	US\$ 0.03	9	12	3.24	3	270	24.3
Rifapentine	US\$ 3	6	12	216	—	—	
Total				219.24			24.3
Labor costs	US\$ 3.5 per hour		12	42		198	693
Medication costs and Labor costs				261.24			717.3

4. Discussion

LTBI treatment is essential for eradicating TB. This study verified that in Taiwan, the administration of a short-term high-dosage rifapentine and isoniazid regimen was significantly more favorable than the standard 9-month isoniazid treatment in terms of medication compliance, treatment completion rate, and economic benefit.

Timely diagnosis and treatment are crucial factors in preventing TB.^[17] The National Tuberculosis Control Program should focus on achieving adequate TB diagnosis and treatment outcomes first, and then prioritize LTBI treatments. Taiwan has a moderately high incidence rate of TB, where the diagnosis rate and treatment outcomes remain undesirable; hence, selective LTBI treatment can serve as a supporting strategy for TB control.^[18] However, according to the FDA, only an average of 60% patients who have received prophylactic treatment (or less) completed the treatment in accordance with their doctors' instructions.^[19] Among the 101 patients who participated in this study, 98 of them completed LTBI treatment (completion rate, 97.03%), which was significantly higher than the completion rate

of the control group (87.29%). This is similar to a large-scale study by Sterling et al, who reported an 82.1% completion rate for the 3-month treatment program and a 69% completion rate for the 9-month treatment program.^[9] We do not know the contribution of DOTS and the shorter regimen both probably contributed to the higher completion rate. Therefore, DOTS seems to be the effective method to monitor LTBI closely as well as to decrease default rate.

Medication side effect was another factor causing patients to discontinue the LTBI treatment course, hepatitis is one of the toxic effects of Isoniazid.^[20] In the control group, among the 590 patients who underwent the 9-month treatment program, 28 of them did not complete their treatment because of side effects. Of the 28 subjects, 21 patients who discontinued their medication presented with elevated GOT/GPT grade 1 to 4. The proportion of subjects with elevated GOT/GPT for the 9-month treatment program (21/28=75%) was substantially higher than that for the 3-month treatment program. Moreover, the discontinuation rate for the 9-month treatment program (4.75%) was also higher than that for the 3-month treatment program (2.97%). These results are similar to that reported by Sterling et al.^[9] Sterling et al^[9] showed that the side-effects ratio of Grade 1, Grade 2, and other side effects observed with the combination therapy was lower than that of the group treated with isoniazid. In the 3HP group, 3 patients who discontinued their medication presented a fever higher than 38.5°C and Grade 2 or 3 toxicity. However, the control group data in our study was obtained from the CDC Central Area Control Center, and the data consisted of only basic patient information and the side effect ratio of the treatment. Indeed, the liver function indices of patients receiving LTBI treatment are important and require continuous monitoring and consideration. Further analysis of the side effects related to the control group and

Table 7**The cost-effectiveness ratio to avoided 1 case of tuberculosis in 3HP group and 9H group.**

	3HP N=98	9H N=515
Cases estimated to become active TB	5	26
Cases actual become active TB	0	2
Cost for one TB case avoided (1 TB case avoided when 20 LTBI cases treated)	\$261.24 per case	\$717.3*(515/24)
	Total \$5225	Total \$15392

the ratio of each side effect requires additional data to be collected.

In addition to the completion rate and side effects, the lower cost of the treatment course is also a crucial consideration with implementation of LTBI treatment. Several large-scale studies have indicated that the efficacy of 3-month rifapentine/isoniazid regimen was similar to that of 9-month isoniazid or 4-month rifampin regimen.^[21–23] Therefore, despite those studies might be accurate in stating that the 9-month isoniazid treatment method is the most economical regimen, they fail to consider the labor costs of DOTS. In Taiwan, DOTS visit LTBI patients 5 days a week for 9 months and spend approximately an hour with each patient. On the other hand, DOTS only need to visit LTBI patients once a week for 12 weeks for 3HP group. In this study, the medication costs of the 3-month and 9-month treatment programs were approximately US\$219.24 and US\$24.30, respectively. Although the 9H medication fee appears less than the 3HP, the labor costs of the 3-month and 9-month programs were approximately US\$42 and US\$693, respectively (Table 6). The cost-effectiveness ratio with isoniazid for 9 months was US\$ 15392/avoided 1 case of tuberculosis and US\$ 5225/avoided 1 case of tuberculosis with 3HP. Therefore, the 3-month treatment was substantially more beneficial (Table 7). Compared with the previous studies in the United States, United Kingdom, and Canada, our study in Taiwan found the similar results that the short-term high-dosage LTBI treatment was cost-effective and associated with higher treatment completion rate. However, we failed to provide data regarding side effects in our control group, which should be collected and analyzed in the future. Overall, we determined that the 3-month program was substantially more economically viable than the 9-month program.

In conclusion, this project is the first study to investigate and compare 2 dissimilar LTBI treatment regimens in the Taiwan area in terms of treatment adherence and the cost. Our results showed that the short-term high-dosage LTBI treatment via DOT improved the treatment completion rate among the TB contacts in this study. Compared with the conventional 9-month LTBI treatment via DOT, the short-term high-dosage treatment method improved patient adherence to the treatment, thereby reducing the chance of disease development. Moreover, this new prophylactic medication could save a considerable amount of labor cost in preventing TB. A large-scale follow-up study will confirm whether this treatment regimen is appropriate for the general population in Taiwan, thereby reducing the disease development rate among TB contacts.

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