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【 ORIGINAL ARTICLE 】

Use of Rifampin Compared with Isoniazid for the Treatment of Latent Tuberculosis Infection in Japan: A Bayesian Inference with Markov Chain Monte Carlo Method

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Abstract:

Objective Treating latent tuberculosis infection (LTBI) is essential for eliminating the serious endemicity of tuberculosis. A shorter regimen is preferred to longer regimens because the former has better adherence with a better safety profile. However, lengthy treatment with isoniazid is still recommended in Japan. Based on the latest evidence, we switched from a conventional nine-month isoniazid regimen to a shorter four-month rifampin regimen for the treatment of LTBI.

Methods To evaluate the safety and efficacy of the shorter regimen, we conducted Bayesian analyses using a stochastic mathematical model to calculate the posterior probabilities of several parameters.

Patients Clinical data of 13 patients in the isoniazid group and 5 in the rifampin group were used for the Bayesian analyses. The outcomes measured were completion of the treatment, adverse effects, number of clinic visits, and medical costs.

Results The medial posterior probability of the isoniazid group completing the treatment was 66% [95% credible interval (CrI) 43-89%], whereas that of the rifampin group was 86% (95% CrI 60-100%). The probability that the completion rate in the rifampin group was better than that in the isoniazid group was as high as 88% (95% CrI 0-100%). Other parameters, such as the number of clinical visits and duration of treatment, were better with rifampin therapy than with isoniazid therapy, with comparable medical costs.

Conclusion Four months of rifampin therapy might be preferred to isoniazid for treating LTBI in Japan.

Key words: latent tuberculosis infection (LTBI), rifampin, isoniazid, Bayesian statistics, Markov Chain Monte Carlo (MCMC) Method

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Background

Tuberculosis places a significant burden on human health and is considered to have infected a third of the global population (1). Among developed nations, Japan has a relatively high incidence of tuberculosis, with about 14 new cases per 100,000 population reported annually (2). Finding and treating people infected with *Mycobacterium tuberculosis* but not showing any clinical symptoms (latent tuberculosis infection, or LTBI) is important for decreasing this burden, and countries such as the United States use this approach to eliminate tuberculosis (3).

There are a number of treatment regimens available for the treatment of LTBI, and all have been shown to be effective; however, shorter regimens are preferred to longer ones because of the higher completion rate and better safety profile. Short-course regimens, such as weekly rifapentine and isoniazid for three months, are endorsed by both the World Health Organization (WHO) and Centers for Diseases Con-

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trol and Prevention (CDC) of the United States (4, 5), although rifapentine is not approved and is thus unavailable in Japan.

A recent multi-national randomized controlled trial showed that four months of rifampin (rifampicin) therapy was not inferior to nine months of isoniazid therapy and had a higher treatment completion rate and better safety profile (6). Based on the available evidence, we switched from the conventional nine-month isoniazid treatment to four-month rifampin therapy as the preferred treatment regimen for LTBI. However, isoniazid therapy is still recommended in Japan, and a majority of patients are treated with this regimen (2, 7). Some experts are reluctant to use rifampin since its use has not been investigated sufficiently in Japan, and concerns regarding the emergence of drug resistance persist.

The application of Bayesian statistics based on Bayes' theorem is gaining popularity in many fields of scientific research (8, 9). While the frequentist approach handles point estimation and asks if a null hypothesis is rejected, the Bayesian estimation method uses an interval estimation approach and determines the likelihood of the null hypothesis being correct. The Bayesian estimation method tells us how likely one group is to outperform another for outcomes, even in cases with a relatively limited number of enrolled patients (8, 9). Therefore, we conducted Bayesian analyses with a stochastic mathematical model to compare rifampin and isoniazid for the treatment of LTBI in Japan to see whether or not rifampin was a reasonable option for treating LTBI in Japan.

Materials and Methods

Participants

Since April 2016, when the Department of Infectious Diseases was founded at Hyogo Prefectural Kakogawa Medical Center, the Department has provided treatment for LTBI in an outpatient setting. From April 2016 to December 2018, a total of 18 patients received treatment of LTBI. Fourteen patients had a diagnosis of LTBI upon initiating immunosuppressants, and four received a diagnosis upon employment. No patient had post-exposure conversion of interferon-gamma assays or others. We enrolled all patients who received treatment for LTBI during the study period in the current analysis.

Exposure

Thirteen patients started with isoniazid therapy, and then the first-line therapy was changed to rifampin for the reason described above. Rifampin was used and completed for five patients with LTBI.

Study model

The primary outcome was the completion rate of the treatment of rifampin better than those of isoniazid. We also investigated other parameters, such as the occurrence of significant adverse effects during the treatment, the number and duration of clinic visits, and medical costs. Adverse reactions were graded as described in a previous study (6).

We constructed Bayesian models as follows: we assumed a Bernoulli distribution for the treatment completion and adverse events, Poisson distribution for the number of clinic visits, and normal distribution for medical costs. We also assumed a non-informative distribution for the prior of each parameter. With data from 18 patients provided, the posterior distributions of parameters were obtained by the Markov chain Monte Carlo (MCMC) method. We set 4 separate sampling sequences, each consisting of 1,000 random samples (including 500 samples discarded for convergence). Sampling convergence was evaluated by Gelman-Rubin statistics and by visually inspecting a trace plot. The region of practical equivalence (ROPE) was arbitrarily determined from -0.1 to 0.1 for the difference in treatment completion and significant adverse events, -2 to 2 for the number of clinic visits, and -1,000 to 1,000 for the cost. The null value is declared to be rejected if the 95% highest density interval (HDI) falls completely outside the ROPE, and the null value is declared to be accepted if the 95% HDI falls completely inside the ROPE.

Because of arbitrary nature of the determined ROPE in our study, sensitivity analyses were performed using different numbers (0.05 to 0.5 by increments of 0.05 for treatment completion and adverse events, 1 to 5 for clinic visits, and 500 to 5,000 for cost by increments of 500 each). All 95% credible intervals (CrIs) were calculated using HDI. We used the R software program, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with a probabilistic programming language Stan (Stan development team) for all Bayesian analyses.

This study was approved by the ethics committee of Hyogo Prefectural Kakogawa Medical Center.

Results

All 18 patients who received LTBI treatment were Japanese citizens. The mean age of the rifampin group was 72.6 ±3.4 years old, and that of the isoniazid group was 69.2± 15.4 years old. Other patient characteristics are summarized in Table 1. Adverse reactions occurred in 5 patients (39%) in the isoniazid group and 2 (40%) in the rifampin group. Three patients (23%) in the isoniazid group switched their medication to rifampin, and 1 stopped it and did not complete the treatment (8%). All patients in the rifampin group were able to complete the treatment without interruption (Table 2). The median duration of the treatment in the isoniazid group was 9 months (range 5-9 months), whereas every patient in the rifampin group had a 4-month treatment duration.

The medial posterior probability of the isoniazid group completing the treatment was 66% (95% CrI: 43-89%), whereas that of the rifampin group was 86% (95% CrI: 60-

Table 1. Patient Characteristics.

Characteristics n, (%)	Rifampin	Isoniazid
Number of the patients	5	13
Age mean (range)	72.6 (68-77)	69.2 (36-93)
Female sex	2 (40)	7 (53.8)
History of exposure to *M. tuberculosis*	1 (20)	3 (23.1)
Underlying medical condition		
RA	4 (80)	7 (53.8)
Polyarthritis of unknown etiology	1 (20)	1 (7.7)
SLE	0	1 (7.7)
Sjögren syndrome	0	1 (7.7)
Chronic leukemia	0	1 (7.7)
None	0	3 (23.1)
Diagnostic test for LTBI		
T spot test	5 (100)	13 (100)
Imaging studies of chest		
Chest X-ray	0	7 (53.8)
CT scan	5 (100)	6 (46.2)
Findings on chest imaging studies		
Normal	0	8 (61.5)
Findings consistent with old TB	1 (20)	3 (23.1)
COPD	2 (40)	0
Nonspecific findings	2 (40)	2 (15.4)
Treatment duration (months) (mean±SD)	4±0	8±1.47
Duration of the follow up of the patients at the study site (months) (mean±SD)	6±1	13.69±8.48
Medical cost JPY (mean±SD)	33,563±12,915	32,969±12,799

RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, CT: computed tomography, TB: tuberculosis, JPY: Japanese yen. Some patients had multiple medical conditions and aggregate of the number does not match the number of the patients.

Table 2. Adverse Reactions during Treatment of LTBI.

Characteristics n, (%)	Rifampin	Isoniazid
Any adverse reactions	2 (40)	5 (38.5)
Grade 1	2 (40)	0
Grade 1-2*	2 (40)	3 (23.1)
Grade 2	0	1 (7.7)
Grade 3	0	1 (7.7)
Grade 4	0	0
Types of adverse reactions		
Liver dysfunction	2 (40)	4 (30.8)
Skin rash or itchiness	1 (20)	1 (7.7)
Fever	0	1 (7.7)
Others	1 (20)	1 (7.7)
Number of treatment change		
Changed to rifampin		3 (23.1)
Changed to isoniazid	0	
Changed to others	0	0
Treatment terminated	0	1 (7.7)

Some patient had more than one adverse reaction so the aggregate of adverse reactions may not match the total number of adverse reactions. *Hepatotoxicity grading was specifically set and combined Grade 1 and 2 to 1-2 based on reference 6.

100%) (Fig. 1). The probability that the completion rate in the rifampin group was better than that in the isoniazid group was as high as 88% (95% CrI: 0-100%). Regarding HDI, 26% fell inside the ROPE. A sensitivity analysis showed it became 13% for ROPE ranging -0.05 to 0.05, and it became 100% when ROPE ranged from -0.5 to 0.5.

The medial posterior probability of the isoniazid group experiencing adverse event was 40% (95% CrI 0-100%), whereas that for the rifampin group was 42% (95% CrI 17-64%), and the probability of the rifampin group having more adverse events was as high as 56% (95% CrI 0-100%). For HDI, 41% of it fell inside ROPE. Sensitivity analysis showed it became 19% for ROPE ranging -0.05 to 0.05, and it became 100% when ROPE ranged from -0.4 to 0.4.

For adverse events requiring initial medication cessation (either switching to another medication or terminating treatment altogether), the medial posterior probability was 33% for the isoniazid group (95% CrI 11-56%) and 14% for the rifampin group (95% CrI 0-41%) (Fig. 2). The probability of adverse reactions necessitating initial drug cessation being more frequent in the isoniazid group than in the rifampin group was as high as 88% (95% CrI 0-100%). For HDI, 25% of it fell inside ROPE. Sensitivity analysis showed it became 10% for ROPE ranging -0.05 to 0.05, and it became 100% when ROPE ranged from -0.5 to 0.5.

The posterior median of the expected number of clinical visits was 7.7 for the isoniazid group (95% CrI 6.4-9.3), whereas that for the rifampin group was 5.2 (95% CrI 3.3-

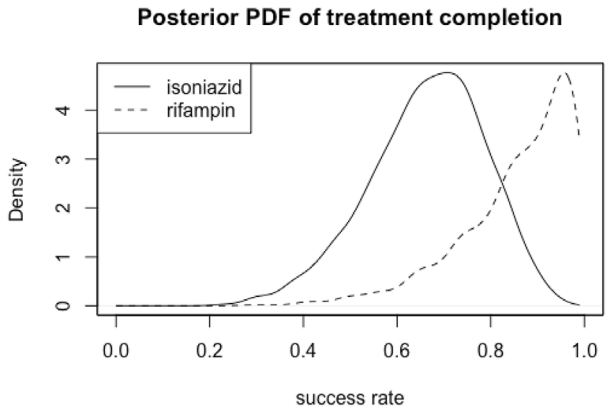

Figure 1. **The posterior probability density function of treatment completion. PDF: probability density function**

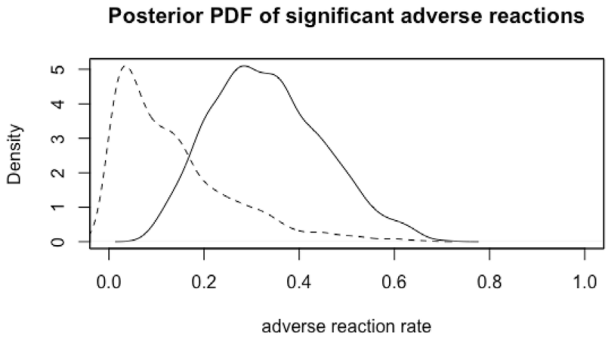

Figure 2. **The posterior probability density function of the occurrence of significant adverse reactions. PDF: probability density function**

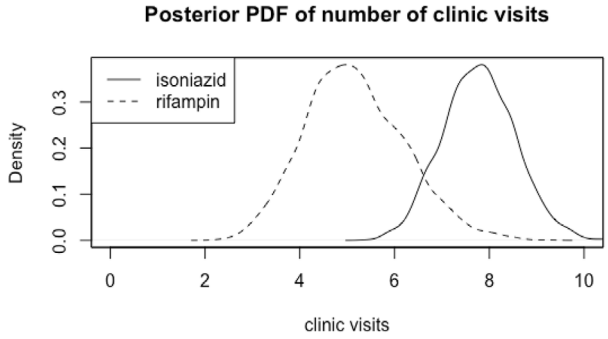

Figure 3. **The posterior probability density function of the expected number of clinic visits. PDF: probability density function**

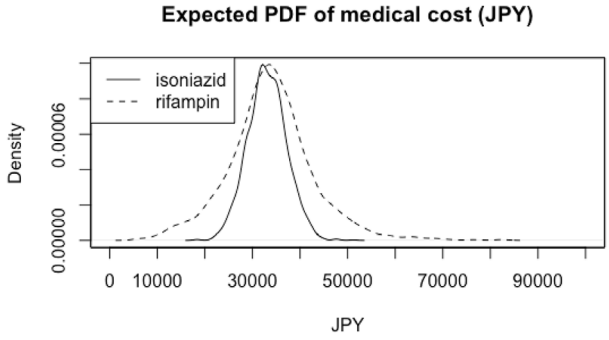

Figure 4. **The posterior probability density function of the expected medical costs. PDF: probability density function, JPY: Japanese yen**

7.3) (Fig. 3). The posterior probability of the isoniazid group engaging in more clinical visits than the rifampin group was as high as 97% (95% CrI 0-100%). For HDI, 27% of it fell inside ROPE. Sensitivity analysis showed it became 7% for ROPE ranging -1 to 1, and it became 100% when ROPE ranged from -5 to 5.

The posterior median of the expected medical costs was 32,920 (95% CrI 24,968-40,821) Japanese yen (JPY) for the isoniazid group and 34,034 (95% CrI 16,849-51,922) JPY for the rifampin group (Fig. 4). The posterior probability of rifampin therapy being more expensive than isoniazid therapy was as high as 53% (95% CrI 0-100%). For HDI, 12% of it fell inside ROPE. Sensitivity analysis showed it became 6% for ROPE ranging -500 to 500, and it was still 50% when ROPE ranged from -5,000 to 5,000.

Convergence was confirmed, with all values of Gelman-Rubin statistics being less than 1.1, and all trace plots also indicated convergence across four chains.

Discussion

Our Bayesian analyses demonstrated the high probability of the superiority of rifampin therapy to isoniazid therapy with respect to treatment completion and the rate of significant adverse events, although the 95% CrIs for each parameter were quite large. The number of clinical visits was also markedly better in the rifampin group than in the isoniazid group, and the expected medical costs were comparable between the two. Rifampin therapy is short and may place much less of a burden on both patients and healthcare professionals. It may also be safer with fewer adverse effects.

Taken together with the findings of a previous study that showed similar results from a large-scale, multi-national randomized controlled trial including many Asian patients (585 from South Korea and 855 from Indonesia) (6), the present findings suggest that it is reasonable to conclude that 4-month treatment with rifampin for Japanese patients with LTBI may be superior to isoniazid therapy. In fact, the frequency of isoniazid resistance in Japan is higher than that of rifampin (3.1% and 0.7%, respectively, for newly treated patients) (10). Based on these present and previous findings, treatment of LTBI using rifampin rather than isoniazid as the first-line therapy should be seriously considered.

Our study does have several inherent limitations. First, our data from a single center might not be generalizable to average LTBI patients in Japan. Second, we did not consider special patient populations, such as children, pregnant women, or those with HIV infection. The treatment of LTBI in those specific populations must be individualized, and our analyses may not be applicable to those patients. Third, the follow-up period differed between the groups in the present

study. The isoniazid group had a longer follow-up period, so the occurrence of adverse reactions after the completion of rifampin may have been ignored. However, the occurrence of rifampin side effects after the completion of treatment is logically and biologically infeasible. Finally, we did not investigate the effectiveness of LTBI treatment in both arms (i.e. the efficacy for preventing active tuberculosis, which is difficult to demonstrate with assumingly very low rate of occurrence of active TB after completion of LTBI treatment).

Conclusion

Our Bayesian analysis with the MCMC method suggested that four months of rifampin therapy might be superior to longer-duration isoniazid therapy for patients with LTBI in Japan. The use of rifampin for the treatment of LTBI over isoniazid, as is practiced in other nations, should be seriously discussed in Japan.

The authors state that they have no Conflict of Interest (COI).

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