



Risk factors for 1-year relapse of pulmonary tuberculosis treated with a 6-month daily regimen



Kyung-Wook Jo^a, Jung-Wan Yoo^a, Yoonki Hong^b,
Jae Seung Lee^a, Sang-Do Lee^a, Woo Sung Kim^a,
Dong Soon Kim^a, Tae Sun Shim^{a,*}

^a Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

^b Department of Internal Medicine, Kangwon National University, Chuncheon, South Korea

Received 8 May 2013; accepted 17 January 2014

Available online 27 January 2014

KEYWORDS

Pulmonary tuberculosis;
2-Month culture conversion;
Cavity;
Relapse

Summary

Background: We aimed to identify the 1-year relapse rate and risk factors for patients with pulmonary tuberculosis (TB) treated with a 6-month daily regimen.

Methods: A total of 317 patients with pan-susceptible pulmonary TB who completed a 6-month daily course of treatment [2HRZ(E)/4HR(E)] were retrospectively analyzed.

Results: The mean age was 50.0 ± 16.8 years and men were predominant (61.2%). All of 137 adults tested for HIV were negative. Six (1.9%) cases relapsed within one year. Relapse rate was higher in patients with a positive culture after 2 months of treatment (10.0%, $p = 0.049$) and in patients with both a positive culture after 2 months of treatment and cavitation on initial chest radiograph (18.2%, $p = 0.015$), whereas relapse rate in patients with cavitation alone was comparable to that of the total population (2.7%). Among various risk factors known to increase risk of relapse, the combined variable of cavitation and positive culture at 2 months (OR = 15.56, 95% CI 2.56–98.71, $p = 0.003$) was only associated with increased relapse rate in a multivariate analysis.

Conclusions: Even with a 6-month daily treatment regimen throughout the intensive and continuation phases, the relapse rate was unacceptably high in patients with both a positive culture at 2 months of treatment and cavitation on baseline chest radiography. Intensification of treatment, such as an extension of treatment duration, should be considered in this category of patients.

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* Corresponding author. Division of Pulmonary & Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Pungnap-Dong, Songpa-gu, Seoul 138-736, South Korea. Tel.: +82 2 3010 3892; fax: +82 2 3010 6968.

E-mail address: shimts@amc.seoul.kr (T.S. Shim).

Introduction

One of the problems of tuberculosis (TB) control is the fact that patients who were successfully treated can relapse, necessitating a second treatment. Reported rates of relapse after standard 6-month treatment for drug-susceptible pulmonary TB have ranged from 1 to 2% at 24 months [1]. Variable parameters such as host factors [2–5], disease factors [6–9], and treatment factors [8,10,11] have been identified as being related to increased relapse rates. Among these, the most important factors are probably positive acid-fast bacilli (AFB) culture on completion of the 2-month intensive phase and cavitation on initial chest radiograph (CXR) [1,6,8,13]. Based on the report that the coexistence of these two factors can increase the risk of relapse up to approximately 20% [6], the American Thoracic Society (ATS) has recommended the minimum duration of treatment should be extended to 9 months for patients with these two risk factors [14].

According to World Health Organization (WHO) guidelines, a daily dosing frequency throughout the course of therapy for new patients with pulmonary TB is optimal [15]. However, in many countries, a 6-month standard regimen is given three times weekly throughout therapy or only in the continuation phase. ATS guidelines regarding the extension of treatment duration to 9 months are also based on a study which revealed increased relapse rate in patients treated with a twice a week regimen for continuation phase treatment [6]. On the other hand, according to Korean national TB guidelines, the recommended treatment for patients with TB is a 6-month daily regimen throughout the course of therapy [16]. Hence, we questioned whether the relapse rate is still high in pulmonary TB patients who had both a 2-month positive culture after treatment initiation and cavitation at baseline and in whom a 6-month short-course treatment was taken daily throughout the course of therapy.

In the present study, we aimed to identify the 1-year relapse rate and associated risk factors for patients with drug-susceptible pulmonary TB treated with a standard 6-month daily regimen in South Korea, an intermediated TB-burden country.

Methods

Study subjects

Study subjects were selected from the TB registry of Asan Medical Center, a 2700-bed referring hospital in Seoul, in South Korea and who were treated between January 2000 and December 2010. Enrollment criteria were as follows: 1) culture-confirmed, pan-susceptible pulmonary TB, 2) follow-up data were available until 1 year after treatment completion, 3) treatment with a standard 6-month daily regimen comprised of 2 months of isoniazid/rifampicin/pyrazinamide/ethambutol and 4 months of isoniazid/rifampicin [2HRZ(E)/4HR(E)], and 4) 2-month culture conversion results were available. In this study subjects, medications were taken daily (7 day/week) throughout the course of therapy according to Korean national TB guidelines [16]. Ethambutol was taken throughout the course of

therapy or until the rapid or conventional drug susceptibility testing (DST) revealed drug-susceptible results according to the attending physician's preference. Directly observed treatment (DOT) was not followed, instead private-public mix cooperation (PPM) nurses monitored the treatment courses [17]. Study subjects were recommended to revisit the clinic at 3–4 months and 12 months after treatment completion. A CXR was taken each time regardless of the presence of symptoms, and sputum AFB smear/culture tests were performed if the CXR showed any suspicion of TB relapse. Relapse was defined as a circumstance in which a patient became or remained culture-negative while receiving anti-TB drugs, but at some point after the completion of therapy became either culture-positive again or experienced clinical, histological and/or radiographic features consistent with active TB, including an appropriate response to retreatment [1].

Patients' demographic and clinical data, TB treatment history, treatment outcomes and 1-year relapse rate were retrospectively reviewed. We followed WHO definitions for treatment outcomes [14]. The Institutional Review Board of Asan Medical Center approved this study (2013-0019).

Radiographic severity was evaluated using the recommendations of the National Tuberculosis Association of the United States [18].

Bacteriological study

AFB smears were examined by Ziehl–Neelsen staining. AFB culture was carried out using solid media alone until July 2007 and then using both solid and liquid media (BACTEC 960 Mycobacterial Growth Indicator Tube; Becton Dickinson, Sparks, MD, USA) thereafter. Conventional DST was performed using the absolute concentration method with Lowenstein–Jensen media at the Korean Institute of Tuberculosis. Pyrazinamide susceptibility was determined using the pyrazinamidase test. Rapid molecular DSTs targeting both isoniazid and rifampicin resistance were also applied in a subset of patients: MTB-Rifa assay (M&D, Wonju, Korea) or GenoType® MTBDR_{plus} assay (Hain Life-science, Nehren, Germany).

Statistical analysis

Comparisons between groups were made using the χ^2 tests for categorical variables. Odds ratio and multiple logistic regression analysis were used to calculate adjusted risk. Independent variables were selected on the basis of their statistical significance. All tests of significance were two sided; $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (version 12.0; SPSS Inc., Chicago, Illinois, USA).

Results

Characteristics of study subjects

Among 836 patients with pan-susceptible pulmonary TB whose 1 year follow up data were available, 519 patients were excluded due to various reasons and 317 patients

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