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Treatment outcomes of rifampin-sparing treatment in patients with pulmonary tuberculosis with rifampin-mono-resistance or rifampin adverse events: A retrospective cohort analysis

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ABSTRACT

Background: Rifampin (RIF) mono-resistant tuberculosis (RMR-TB) is a rare disease. Current guidelines recommend that RMR-TB be treated as multidrug-resistant TB (MDR-TB) but the evidence is scarce.
Methods: We conducted a retrospective cohort study on pulmonary TB patients to investigate the characteristics and outcomes of RMR-TB. The characteristics of RMR-TB were compared with those with adverse events to rifampin (RAE-TB).
Results: Forty-four RMR-TB and 29 RAE-TB patients were enrolled. RMR-TB patients showed more alcohol use, prior history of TB, and radiologically severe disease, while RAE-TB patients were older and had more comorbidities and combined extrapulmonary TB. A fluoroquinolone (FQ) was the drug most commonly added (70.5%, RMR-TB; 82.8%, RAE-TB). Median treatment duration was 453 days in RMR-TB and 371 days in RAE-TB ($p = 0.001$) and treatment success rates were 87.2% (34/39) and 80.0% (20/25), respectively ($p = 0.586$). Subanalysis of the RMR-TB group by treatment regimen (standard regimen [n = 11], standard regimen + FQ [n = 12], MDR-TB regimen [n = 21]) revealed a higher rate of radiologically severe disease in the MDR-TB subgroup, with similar treatment success rates for the subgroups (85.7% [6/7]), 91.7% [11/12], and 85.0% [17/20], respectively) despite different durations of treatment (345, 405, and 528 days, respectively). Two recurrences (33.3% [2/6]) developed only in standard regimen subgroup, suggesting that standard regimen is not enough to treat RMR-TB patients.
Conclusions: The treatment outcome of RMR-TB with 1st-line drugs + FQ was comparable to that of MDR-TB regimen. Shorter treatment duration may be considered for RMR-TB patients compared with MDR-TB patients.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is still a leading cause of death worldwide resulting in 1.5 million TB deaths in 2014 [1]. Rifampin (RIF or R) is a bactericidal agent that constitutes the backbone of short course anti-TB chemotherapy regimen, but concern about the emergence of drug-resistant strains is growing [2].

RIF-mono-resistant TB (RMR-TB) is a rare disease that represents 0.8% of new TB cases and 2.1% of relapsed cases in Korea. Among 8840 new TB cases diagnosed between 1994 and 2004, 266 cases (3.0%) were resistant to RIF and only one-fifth of them were RMR-TB [3]. Most (approximately 74–83%) [4,5] of *M. tuberculosis* strains that are resistant to RIF are also resistant to isoniazid (INH or H); infection by such strains defines multidrug-resistant TB (MDR-TB). RIF resistance is often regarded as a proxy for MDR-TB due to its rarity, but the impact and the management of RMR-TB have not been as widely studied as they have for MDR-TB.

The World Health Organization (WHO) [6] and the International Union Against Tuberculosis and Lung Disease (IUATLD) [7] recommend that RMR-TB should be treated as MDR-TB for at least 20 months, with INH being added to the regimen until drug susceptibility test (DST) results to INH are available. However, the

Abbreviations: AFB, acid-fast bacilli; DST, drug susceptibility test; DOT, directly observed treatment; FQ, fluoroquinolone; HIV, human immunodeficiency virus; IQR, interquartile range; MDR, multidrug-resistant; RAE, rifampin adverse events; RIF, rifampin; RMR, rifampin mono-resistant; TB, tuberculosis.

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evidence supporting such a recommendation is weak. Some experts recommend 18-month regimens comprising INH, pyrazinamide (PZA or Z), and ethambutol (EMB or E), with or without a fluoroquinolone, on the basis of clinical experience [8].

Previous studies on RMR-TB mainly focused on the epidemiology and risk factors, while few investigated treatment regimens or treatment outcomes of RMR-TB [9–12]. Stagg et al. pointed out that there has been no randomized controlled study that focused solely on the treatment of RIF-resistant TB [13]. We conducted a retrospective cohort study on pulmonary TB patients to investigate the characteristics and treatment outcomes of RMR-TB. In addition, in order to evaluate the appropriate treatment regimen and treatment duration using RIF-sparing regimens, patients who had discontinued RIF due to adverse events were also included in this study.

2. Materials and methods

We conducted a retrospective cohort study of pulmonary RMR-TB patients treated in a tertiary referral center, Asan Medical Center, Seoul, Korea, from January 1999 to December 2013. Patients with pan-susceptible TB who had discontinued RIF due to adverse events (RAE-TB) were also selected and the clinical characteristics and treatment outcomes were compared between two groups.

2.1. Definitions and inclusion criteria

Patients who had pulmonary TB with available DST results were included in the study. Patients were at least 15 years of age and had treatment started with a standard regimen comprised of HREZ or HRE. A patient with both pulmonary and extrapulmonary TB was classified as a case of pulmonary TB [14].

Generally, RMR is defined as a resistance to RIF without resistance to any other first-line anti-TB drugs. However, in this study, RMR-TB was defined as TB caused by a *M. tuberculosis* strain with RIF resistance and INH susceptibility on DST, regardless of other drug resistance pattern. Patients with pan-susceptible TB on DST who had experienced RIF-related adverse events and discontinued RIF within 2 months were assigned to the RAE-TB group.

Treatment outcomes were defined following the WHO definitions on RIF-resistant or MDR-TB. Patients who were not started on a MDR-TB regimen were assigned an outcome from those for RIF-susceptible TB [6]. Unfavorable outcomes include treatment failure, died, lost to follow-up, recurrence and acquisition of drug resistance other than to RIF.

2.2. Bacteriological study

Acid-fast bacilli (AFB) smears were examined by Ziehl-Neelsen staining. AFB culture was carried out using solid Ogawa 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 Lowënstein-Jensen media at the Korean Institute of Tuberculosis. The drug concentrations for susceptibility testing were 0.2 μg per milliliters (μg/mL) for INH, 40 μg/mL for RIF, and 2 μg/mL for EMB. Pyrazinamide susceptibility was determined using the pyrazinamidase test.

2.3. Patient characteristics

We reviewed the patients' electronic medical records and collected baseline characteristics including age, sex, body-mass index (BMI), alcohol use, smoking history, comorbidities including human immunodeficiency virus (HIV) infection, prior treatment history of TB, sputum smear results, radiologic severity, presence of cavities on chest radiograph, and combined extrapulmonary TB infections. Radiographic severity was categorized into minimal, moderately advanced, or far advanced according to the criteria proposed by the U.S. National Tuberculosis and Respiratory Disease Association [15].

Treatment outcomes were reassessed in each of the patients according to the WHO definitions, and total treatment duration, treatment duration of each anti-TB drug, acquisition of drug resistance, and recurrence were examined.

The RMR-TB patients were divided into three subgroups according to the treatment regimen; standard regimen (HRE or HREZ), standard regimen plus fluoroquinolone (FQ), and INH plus MDR-TB regimen. We compared the treatment outcome and treatment duration of each subgroup.

2.4. Statistical analyses

Statistical analyses were performed by SPSS statistics version 21. Analysis of categorical variables was done using the chi square test and Fisher's exact test and continuous variables were analyzed by independent *t*-test and Mann-Whitney test. Treatment outcomes of the three RMR-TB subgroup according to the treatment regimen were compared using Kruskal-Wallis H-test and linear-by-linear association, and the treatment duration was compared using analysis of variance (ANOVA) models. For the ANOVA models, post hoc analysis was done using the Bonferroni correction method. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Fifty-six patients with RMR-TB and 259 patients with RAE-TB who were treated at our hospital from January 1999 to December 2013 were identified. Of the 56 patients with RMR-TB, 12 patients not treated initially with the standard regimen were excluded, for a total enrollment of 44 RMR-TB patients. Of 259 patients with RAE-TB, 52 who were not treated initially with the standard regimen, 59 without available DST, and 119 patients treated with RIF for more than 2 months were excluded, for a total enrollment of 29 RAE-TB patients.

The baseline characteristics of the two groups were compared (Table 1). The RMR-TB patients were younger and had more alcohol use, prior history of TB and radiologically more severe disease compared with the RAE-TB patients. The RAE-TB patients were older and had more comorbidities and combined extrapulmonary TB than the RMR-TB patients. The remaining patient characteristics, including sex, BMI, proportion of ever-smoker and HIV infection status, and sputum positivity were not different between the RMR-TB and RAE-TB groups. Three RMR-TB patients were resistant to EMB and six were resistant to PZA: one of them had both EMB and PZA resistance. No patients enrolled in this study had resistance to fluoroquinolones.

3.2. Treatment regimens and durations

Daily treatment was prescribed during the whole treatment duration. Treatment was not directly observed but instead specialized private-public-mix (PPM) cooperation nurses monitored the treatment courses. Comparison of treatment duration of each anti-TB medication in the RMR-TB and RAE-TB groups is shown in Table 2. INH, PZA, injectable drugs, and some of the second-line oral drugs were prescribed longer in the RMR-TB