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The efficacy of rifabutin for rifabutin-susceptible, multidrug-resistant tuberculosis

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Summary
Objective: We investigated the efficacy of rifabutin (RFB)-containing regimens for the treatment of RFB-susceptible, multidrug-resistant tuberculosis (MDR-TB).
Methods: From 146 patients diagnosed with MDR-TB between January 2006 and December 2009 at Asan Medical Center in South Korea, 31 patients (21.2%) were found to have RFB-susceptible MDR-TB. Of these 31 patients, 14 patients who had been treated with RFB for more than one month were included. Forty-two patients with RFB-resistant MDR-TB were selected as a control group, and the outcomes of both groups were retrospectively compared.
Results: Of 14 patients with RFB-susceptible MDR-TB, the mean age was 44.4 years and the proportion of extensively drug-resistant TB (XDR-TB) was 35.7% (5/14). Baseline characteristics and the drug resistance pattern (except RFB) did not differ between the two groups. Treatment success was achieved in 12 (85.7%) patients in the RFB group: cure in 10 (71.4%) and treatment completion in two (14.3%). The treatment success rate was 52.4% (22/42) in the control group ($p = 0.032$). Treatment failure was more common in patients of the control group (40.5% vs. 14.3%; $p = 0.106$).
Conclusions: RFB is useful as an additional drug in the treatment of MDR-TB in patients with RFB-susceptible MDR-TB.

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Introduction

Multidrug-resistant tuberculosis (MDR-TB) affects people in all regions of the world and remains a serious threat to public health.[1] In addition, the appearance of extensively drug-resistant TB (XDR-TB), a subset of MDR-TB, has complicated both the treatment and control of the disease.[2] In South Korea, an intermediate TB-burden country, 2.7% of patients newly diagnosed with TB and 14% of patients with a history of previous TB treatment were found to have MDR-TB in 2004.[3] Additionally, XDR-TB is estimated to occur in approximately 5—10% of the patients with MDR-TB.[4] In South Korea, the overall treatment success rate has been reported to be 45.3% among 1407 patients with MDR-TB and only 29.3% among patients diagnosed with XDR-TB.[5] Despite the global effort to control MDR-TB, few new drugs have been developed to treat it since 1970.

Rifabutin (RFB) is a first-line anti-TB drug which is reserved for patients with drug-susceptible TB and who are taking medications incompatible with rifampicin (RIF), such as antiretroviral drugs.[6,7] Although RFB may have comparable rates of cure and relapse as those of RIF in the treatment of drug-susceptible TB,[8,9] few data on the efficacy of RFB in the treatment of MDR-TB are available.[10,11]

Although the level of cross-resistance between RIF and RFB has been reported to be approximately 90%,[12,13] it is known to be relatively low in South Korea, with as many as 20—30% of patients with RFB-susceptible MDR-TB.[14,15] Thus, RFB might be a successful drug for the treatment of a subset of MDR-TB. However, to date there has not been any study conducted to address this issue in South Korea. Therefore, we retrospectively investigated the role of RFB in the treatment of RFB-susceptible MDR-TB.

Methods

Study subjects

Because drug susceptibility testing (DST) to RFB began in South Korea in 2006, our study subjects were selected from the MDR-TB registry of Asan Medical Center between January 2006 and December 2009. A total of 146 patients were diagnosed with MDR-TB during this period. Among them, 31 (21.2%) had RFB-susceptible TB, of whom 15 were treated with RFB-containing regimens. The baseline clinical characteristics and drug resistance patterns did not differ between the 15 RFB users and the 16 RFB non-users (data not shown). Among these 15 patients, one was excluded based on less than one month of treatment with RFB due to an adverse event (severe myalgia), leaving 14 patients with RFB-susceptible MDR-TB enrolled. The patients' medical records, TB treatment history with regard to World Health Organization (WHO) guidelines, DST results, treatment modality, and outcomes were retrospectively reviewed.

Using a nested case-control design, we selected 42 subjects from patients with MDR-TB whose DST showed resistance to RFB during the same period to be the control group. This ensured both groups would have an identical drug resistance pattern except for RFB.

Definitions of study measures

Classifications of drug resistance pattern

Four groups were defined as follows[5]: (1) XDR-TB was defined as MDR-TB with bacillary resistance to any one of the fluoroquinolones (FQ) and to at least one of three, second-line injectable drugs (SLID, i.e. amikacin, capreomycin, or kanamycin); (2) pre-XDR-TB_{FQ} as MDR-TB resistant to any FQ; (3) pre-XDR-TB_{SLD} as MDR-TB resistant to at least one SLID; and (4) other MDR-TB as MDR-TB not resistant to both FQ and SLID.

Treatment outcomes

Six treatment outcome categories, i.e. cure, treatment completion, treatment failure, transfer out, default, and death were defined.[16] Treatment success was defined as either cure or treatment completion. As recommended by the WHO, all treatment outcomes were based on AFB (acid-fast bacillus) culture results. The duration of adequate treatment was defined as 18 months or more and 12 months or more after culture conversion.

Radiologic severity

Radiographic severity was estimated using the recommendations of the National Tuberculosis Association of the United States.[17]

Drug susceptibility tests

Conventional DST was performed using the absolute concentration method with Lowënstein—Jensen (LJ) media for isoniazid, RIF, ethambutol, pyrazinamide, streptomycin, kanamycin, cycloserine, *p*-aminosalicylic acid, prothionamide, ofloxacin, and moxifloxacin at the Korean Institute of Tuberculosis, South Korea's supranational TB reference laboratory. The critical concentration level of RFB was set at 20 μg/mL, which is a half the value of RIF (40 μg/mL). Growth greater than 1% of the control was regarded as drug resistance.[15]

Statistical analysis

All analyses were performed using SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). Comparisons between the RFB group and the control group were made using Mann—Whitney tests for continuous variables and χ^2 test or the Fisher's exact test for categorical variables. All tests of significance were two sided; $p < 0.05$ was considered statistically significant.

Results

Characteristics of study subjects

Of the 14 patients in the RFB group, five (35.7%) were defined as having XDR-TB, six (42.9%) with pre-XDR-TB_{FQ}, one (7.1%) with pre-XDR-TB_{SLD}, and two (14.3%) with other MDR-TB. The 42 patients in the control group had the same proportion of drug-resistance pattern as that of the RFB group (Table 1). Baseline characteristics such as age, sex,