



Treatment outcomes of rifabutin-containing regimens for rifabutin-sensitive multidrug-resistant pulmonary tuberculosis



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ARTICLE INFO

Article history:

Received 17 August 2017

Received in revised form 14 October 2017

Accepted 18 October 2017

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Multidrug-resistant tuberculosis
Extensively drug-resistant tuberculosis
Rifabutin
Treatment outcome

ABSTRACT

Objectives: The aim of this study was to evaluate whether rifabutin can improve treatment outcomes in patients with rifabutin-sensitive MDR-TB.

Methods: A retrospective cohort study was performed on 76 patients with rifabutin-sensitive MDR-TB who were treated with or without rifabutin between 2006 and 2011.

Results: Overall, 75% (57/76) of patients achieved favorable outcomes, including cure (53/76, 70%) and treatment completion (4/76, 5%). In contrast, 25% (19/76) had unfavorable treatment outcomes, which included treatment failure (6/76, 8%), death (2/76, 3%), loss to follow-up (4/76, 5%), and no evaluation due to transfer to other institutions (7/76, 9%). Rifabutin was given to 52 (68%) of the 76 patients with rifabutin-sensitive MDR-TB. Although favorable treatment outcomes were more frequent in patients who received rifabutin [81% (42/52)] than in those who did not receive rifabutin [63% (15/24)], this difference was not statistically significant ($P=0.154$). However, in multivariable regression logistic analysis, use of rifabutin was significantly associated with favorable treatment outcomes in patients with rifabutin-sensitive MDR-TB (adjusted odds ratio=9.80, 95% confidence interval=1.65–58.37, $P=0.012$).

Conclusions: These results suggest that the use of rifabutin can improve treatment outcomes in patients with rifabutin-sensitive MDR-TB.

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Introduction

Despite substantial efforts to reduce the global burden of multidrug-resistant tuberculosis (MDR-TB), which is defined as TB with resistance to isoniazid and rifampin, the treatment outcomes of MDR-TB are unsatisfactory (Ahuja et al., 2012; Bastos et al., 2017; Falzon et al., 2017). For individualized treatment regimens for patients with MDR-TB, the World Health Organization (WHO) currently recommends that at least five effective anti-TB drugs be administered during the intensive phase, including pyrazinamide and four second-line TB medications (Falzon et al., 2017). However, development of a treatment regimen composed of five effective drugs is challenging (Jeon, 2015). Therefore, in cases where the recommendations for five effective drugs cannot be met due to

drug resistance or side effects, additional drugs that can be used need to be identified (Chang et al., 2013; Dooley et al., 2013; Fox et al., 2017).

Rifabutin is a first-line anti-TB drug for the treatment of drug-sensitive TB and is especially useful in patients who cannot tolerate rifampin, i.e., those who take medications that interact with rifampin or those who experience side effects from rifampin (Nahid et al., 2016). Although cross-resistance to rifampin and rifabutin is common in MDR-TB cases, some studies have shown that a considerable proportion (about 20–30%) of rifampin-resistant MDR-TB and even extensively drug-resistant (XDR)-TB isolates still have *in vitro* susceptibility to rifabutin (Berrada et al., 2016; Chien et al., 2000; Dheda et al., 2017b; Dickinson and Mitchison, 1987; Senol et al., 2005; Sirgel et al., 2013; Uzun et al., 2002). These results suggest that rifabutin might have clinical efficacy against rifabutin-sensitive MDR/XDR-TB (Dheda et al., 2017a). However, information on the clinical usefulness of

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rifabutin in the treatment of rifabutin-sensitive MDR-TB is very limited (Jo et al., 2013; Lee et al., 1996). The aim of this study was to evaluate whether rifabutin can improve treatment outcomes in patients with rifabutin-sensitive MDR-TB.

Patients and methods

Study population

The medical records of 76 consecutive patients with rifabutin-sensitive MDR-TB, from a cohort of pulmonary MDR-TB patients treated between January 2006 and December 2011 at Samsung Medical Center (a 1,961-bed referral hospital in Seoul, South Korea), were evaluated (Jeong et al., 2015). This study was approved by the Institutional Review Board of Samsung Medical Center (IRB number 2014-03-007). Informed consent was waived because of the retrospective nature of this study, and patient information was anonymized and de-identified prior to analysis.

Drug susceptibility testing (DST)

DST was performed using the absolute concentration method with Löwenstein–Jensen medium at the Korean Institute of Tuberculosis (Bai et al., 2007). In our hospital, all first isolates of *M. tuberculosis* from each patient with culture-confirmed TB are referred for DST. DST was routinely performed for WHO group-1 drugs (isoniazid, rifampin, rifabutin, ethambutol, and pyrazinamide); group-2 drugs (streptomycin, kanamycin, and capreomycin); group-3 drugs (ofloxacin, moxifloxacin); and group-4 drugs [prothionamide, cycloserine, and para-aminosalicylic acid (PAS)] over the study period (WHO, 2014). DST for amikacin and levofloxacin became established in 2007 and 2009, respectively. The critical concentration for resistance for rifabutin was 20 µg/mL (Jo et al., 2013). Effective drugs were defined as those drugs to which the isolates were susceptible. Otherwise, drugs were categorized as “used drugs”. As DST for WHO Group 5 drugs (linezolid, amoxicillin/clavulanate, and clarithromycin) was not performed during the study period, these drugs were categorized as used drugs. Additionally, since the effectiveness of rifabutin for the rifampin-resistant/rifabutin-susceptible isolates was being determined in this study, rifabutin was categorized as a used drug and not as an effective drug in patients with rifabutin-susceptible MDR-TB.

Treatment modalities

All patients received individualized treatment regimens composed of at least four effective drugs, in accordance with previously published WHO guidelines (WHO, 2008). When an individualized regimen with four effective drugs could not be developed, we added WHO group-5 drugs to the treatment regimen. The treatment duration was 18–24 months, including at least 12 months after culture conversion. An injectable agent was prescribed for at least six months, including a minimum of four months after culture conversion for the intensive phase treatment. During the study period, the use of rifabutin was decided at the discretion of the attending physician. Patients who were administered rifabutin received 300 mg/day. Sputum smear and culture tests were performed monthly for the first six months, and then repeated at two- to three-month intervals until the end of treatment. Surgical resection was generally performed for patients with MDR-TB that was refractory to or highly suspected to be unresponsive to medical treatment on the basis of resistance patterns and in those patients with a localized lesion with a high bacterial burden (a cavity or cavities) (Jeong et al., 2015).

Treatment outcomes

Treatment outcomes were defined based on the revised 2013 WHO recommendations (WHO, 2013). A patient was defined as cured when the patient completed treatment, without treatment failure, with at least three consecutive negative culture results separated by at least 30-day intervals after the intensive phase. Treatment completion was defined as when the patient completed treatment, without evidence of treatment failure, but there was no record to indicate that three or more consecutive cultures taken at least 30 days apart were negative after the intensive phase. Treatment failure was defined as a permanent change in treatment regimen due to (1) lack of conversion at the end of the intensive phase, (2) bacteriological reversion in the continuation phase after negative conversion, (3) additional acquired resistance to fluoroquinolones (FQs) or second-line injectable drugs (SLIDs), or (4) adverse drug responses. When a different treatment regimen was initiated for a case with treatment failure, the patient was allocated a new cohort number and treatment category. “Cured” and “treatment completed” were considered favorable treatment outcomes. Other outcomes were classified as unfavorable outcomes.

Statistical analysis

Data are presented as numbers (%) for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Categorical variables were compared using the χ^2 test with Yates continuity correction. Continuous variables were compared using the Mann–Whitney *U* test. To evaluate whether a rifabutin-containing regimen was associated with favorable treatment outcomes, a multivariable logistic regression analysis was performed with backward selection method with $P > 0.10$ for removal of variables, with mandatory inclusion of age, diabetes mellitus status, chronic liver disease status, sputum positivity for acid-fast bacilli (AFB), resistance to FQ, and use of rifabutin in the final models. Initial variables entered into the model included: the variables mandatorily included in the final models (age, diabetes mellitus status, chronic liver disease status, sputum AFB positivity, resistance to FQ, and use of rifabutin); previous treatment of TB; cavitory lesions in chest radiographs; duration of the intensive phase of treatment; number of effective drugs; use of injectable drugs; use of cycloserine; and use of PAS. In the final model, age, diabetes mellitus status, chronic liver disease status, previous treatment of TB, sputum AFB positivity, resistance to FQ, intensive phase duration, number of effective drugs, and use of rifabutin were included. A two-sided P value < 0.05 was considered to be statistically significant. All statistical analyses were evaluated using R 3.3.0 (Vienna, Austria; <http://www.R-project.org/>).

Results

Baseline characteristics

The baseline characteristics of the 76 patients are summarized in Table 1. Of the 76 patients, 39 (51%) were male with a median age of 35 years (IQR, 29–50 years). The most common comorbidities were diabetes mellitus (7/76, 9%) and chronic liver disease (5/76, 7%). Seventy-five patients (99%) were tested for human immunodeficiency virus infection, none of whom tested positive. Whereas 10 patients (13%) had no previous TB treatment history, 66 (87%) had a previous TB treatment history of first-line drugs ($n = 28$) and second-line drugs ($n = 38$). Cavitory lesions were observed by chest radiography in 36 patients (47%). Sputum AFB smear tests were positive in 49 patients (65%). Based on drug-resistance patterns for FQs and SLIDs, 35 patients (46%) had FQ-sensitive, SLID-sensitive

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