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Low Doses of Rifampicin Used in New Tuberculosis Patients Correlated to Increased Frequency of Rifampicin-Resistance and Poorer Treatment Outcomes

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Abstract

The prognosis of patients with previously treated tuberculosis (TB) was suggested to be dependent on whether the initial treatment was in compliance with the established guidelines. The aim of this retrospective multicenter study was to determine the proportion of new TB patients who received standard doses of rifampicin in multiple provinces of China, and the relationship between low doses of rifampicin and frequency of rifampicin-resistance as well as treatment out-

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comes. A total of 713 new TB patients were treated with either once-daily dose of bulk anti-TB drugs (group I) or every other day combination blister packs of anti-TB drugs containing rifampicin (group II) at more than 30 TB treatment centers/hospitals in China. Treatment history, therapeutic doses of rifampicin, and information about patients were extracted from their medical records and analyzed, and rifampicin-resistance of isolates collected from patients following the treatment as well as treatment outcomes were compared between two treatment groups. Among 522 patients in treatment group I, 154 (29.5%) received standard and 363 (69.5%) received low doses of rifampicin; 238 (45.6%) isolates were rifampicin-resistant, and 243 (46.6%) were successfully treated. Among 191 patients in treatment group II, 175 (91.6%) received standard and 15 (7.9%) received low doses of rifampicin; 72 (37.7%) isolates were rifampicin-resistant, and 105 (55%) were successfully treated. When patients who received low doses of rifampicin were compared to others within the same treatment group, increased rates for rifampicin-resistance and treatment failure were observed. Results from this study showed that most new TB patients in treatment group I (69.5%) received low doses of rifampicin, and their treatment outcomes were worse than those in treatment group II, indicating that low doses of rifampicin used for the initial treatment of new TB patients were correlated to increased frequency of rifampicin-resistance and poorer treatment outcomes.

Keywords

***Mycobacterium tuberculosis*, Rifampicin, Therapeutic Doses, Drug Resistance, Treatment Outcomes**

1. Introduction

Tuberculosis (TB) is one of the leading infectious diseases in the world. An estimated 9.0 million people developed TB in 2013 and 0.48 million of them were multidrug-resistant (MDR)-TB [1]. To improve treatment outcomes and prevent the transmission of drug-resistant *Mycobacterial tuberculosis* (*M.tb*), it is crucial to treat new cases of pulmonary TB with standard doses of four first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) [2] [3]. Each of the four first-line anti-TB drugs plays an important role in the treatment of TB and rifampicin is one of the most effective anti-TB drugs [3].

Previous studies suggested that the prognosis of patients with previously treated pulmonary TB was dependent on whether or not the initial treatment of new cases was in compliance with the established guidelines [2]-[5], and the risk of developing drug-resistant TB and MDR-TB was increased dramatically in patients who received inadequate treatments [6]. Previous studies also indicated that one of the factors causing drug resistance could be the insufficient dose of drugs given to TB patients [7], that the plasma concentration of rifampicin was related to the body weight of patients, and that increased body weight could reduce the plasma concentration of rifampicin [8] [9]. When high-verse standard-doses of rifampicin used in Indonesia patients with pulmonary TB were compared, the mean peak plasma concentration of rifampicin in the high-dose (600 mg) group was found to be higher than that in the standard-dose (450 mg) group and the difference was statistically significant, whereas the enzyme activity of glutamic-pyruvic transaminase between two groups had no significant difference [10]. Recently published studies also showed that bioavailability of rifampicin in four out of five fixed-dose combinations used in China was not within the acceptable therapeutic range of 80% - 125% [11], that three two-drug fixed-dose combinations used in a clinical trial in China displayed inferior rifampicin bioavailability compared with the reference drug [12], and that increasing the rifampicin concentration could inhibit the growth of rifampicin-resistant *M. tuberculosis* in vitro [13].

In this retrospective multicenter study, we aimed to determine the proportion of new TB patients who received standard doses of rifampicin in multiple provinces of China and the relationship between low doses of rifampicin used for the initial treatment of new TB patients and frequency of rifampicin-resistance as well as treatment outcomes.

2. Methods

2.1. Setting and Study Population

The Medical Ethics Committee at Beijing Chest Hospital approved this study before the study began, and written informed consent forms were signed by participants for their clinical records to be used in this study. Patients diagnosed as sputum smear positive (acid-fast bacilli staining) and culture positive pulmonary TB were treated previously with bulk drugs or combination blister packs of anti-TB drugs at more than 30 TB prevention and treatment centers/hospitals in multiple provinces of China between July 2009 and July 2011. The selection criteria of patients included those who were diagnosed as active pulmonary TB and treated previously. Patients were ineligible for this retrospective multicenter study if they had non-TB mycobacterial lung diseases, combined extrapulmonary TB, combined severe diseases in heart, liver and kidney, malnutrition, human immunodeficiency virus (HIV), diabetes complications, pneumoconiosis, blood disorders, digestive diseases, etc. Patients were also excluded if their records were incomplete.

For the initial treatment of new TB patients, physicians at specialized TB hospitals usually prescribe once-daily doses of bulk anti-TB drugs including rifampicin (300 - 750 mg) individually to patients according to their different circumstances (group I). Whereas, health care providers at TB prevention and treatment centers (or local sites of the Chinese CDC) generally use combination blister packs of anti-TB drugs containing 600 mg of rifampicin as the intermittent therapy every other day for new TB patients (group II). Patients in both groups received an initial phase of two-month oral regimens of four first-line anti-TB drugs followed by a continuation phase of about four months using isoniazid and rifampicin.

2.2. Data Collection

Staff involved in collection of data from patients, culture of sputum samples collected from TB patients in two treatment groups following the treatment on Löwenstein-Jensen (L-J) solid media (purchased from the same supplier), drug susceptibility testing (DST) on collected isolates with *M. tuberculosis* strain H37Rv as the control, and submission of data online at each center were trained by experts using the same training materials and standard operation protocols.

A standard web-based questionnaire was created specifically for this study to extract a variety of data about TB patients who were treated between July 2009 and July 2011 in two treatment groups at more than 30 TB prevention and treatment centers/hospitals in multiple provinces of China. The data including previous treatment history, therapeutic doses of rifampicin used in the initial treatment, DST results against rifampicin for isolates collected from patients following the treatment, treatment outcomes, plus gender, age, and body weight of patients at the time of the initial treatment were extracted from patients' medical records at each participating center or hospital. After collection at each participating center, data were uploaded immediately to the main server located in Beijing Chest Hospital. Completed reports were reviewed and verified by the project manager, and selected for this study if they met the inclusion criteria.

2.3. Data Analysis

According to the established guidelines [2]-[5], standard doses of rifampicin should be: 450 mg per day for patients weighting <50 kg and 600 mg per day for patients weighting ≥50 kg with 600 mg as the maximal daily dose for patients in treatment group I; and 600 mg per day for patients in treatment group II who weight either <50 kg or ≥50 kg. Collected data were analyzed and compared to determine what proportions of patients in each group were in compliance with the standard doses of rifampicin and to find the correlation between low doses of rifampicin used for the initial treatment of new TB patients and frequency of rifampicin-resistance as well as treatment outcomes. Data management and statistical analysis were performed using the SPSS 17.0 software. The Fisher's Exact Test Calculator for two × two Contingency Tables (http://research.microsoft.com/en-us/um/redmond/projects/mscompbio/fisherexacttest/) and Pearson's chi-square test were used to analyze and compare categorical variables, and $P<0.05$ was considered statistically significant.

3. Results

A total of 713 patients with previously treated smear positive pulmonary *M. tuberculosis* were selected for this

retrospective multicentre study (**Table 1**). The number of male patients (527) was significantly higher than that of female patients (186), which was consistent with the 2010 National Epidemiological Survey of China [14]. The age ranges of patients were from 12 to 87 years old and 673 of them (94.4%) were between the age of 20 and 59; the range of body weight was from 32.5 kg to 115 kg with the average body weight of 56.5 kg, and 475 of them (66.6%) were between body weight of 50 and 70 kg (**Table 1**). Out of 522 patients in treatment group I, 154 (29.5%) received standard doses of rifampicin, 363 (69.5%) received low doses of rifampicin, and five (1.0%) were overdosed (**Table 2**). As shown in **Table 2**, 74.6% of male patients received low doses of rifampicin which was significantly higher than that of female patients (55.7%). There was a significant difference in proportion of patients received standard doses of rifampicin between patients weighing below 50 kg (90.9%) and equal or above 50 kg (13.1%). Out of 191 patients in treatment group II, 175 (91.6%) received standard doses and 15 (7.9%) received low doses of rifampicin, and only one (0.5%) received high dose of rifampicin (**Table 3**). There was no significant difference in proportion of patients received standard doses of rifampicin among different age groups from 20 to 70 and older ($P = 0.462$) and patients with different body weight ($P = 0.336$).

To determine whether low doses of rifampicin used in the initial treatment of new TB patients were correlated to increased frequency of rifampicin-resistance and poorer treatment outcomes in previously treated TB patients, we compared the number of patients who were treated with low doses of rifampicin, the frequency of rifampicin-resistance and treatment outcomes between two treatment groups following the treatment. As indicated in **Table 4**, 69.5% of patients (363/522) in treatment group I, and 7.9% of patients (15/191) in therapeutic group II were initially treated with low doses of rifampicin; and the difference between two groups was statistically significant ($P < 0.0001$).

Results from drug susceptibility testing (DST) conducted on *M.tb* cultures collected following the treatment showed that 45.6% of clinical isolates (238/522) collected from TB patients in treatment group I and 37.7% of clinical isolates (72/191) collected from TB patients in treatment group II were resistant to rifampicin, and the difference between two groups was statistically significant ($P < 0.0304$). We also observed that rifampicin-

Table 1. Demographic characteristics of study participants in two treatment groups.

Characteristics	Patient no. (%)	Group I[a] (%)	Group II[b] (%)
Gender			
Male	527 (73.9)	382 (73.2)	145 (75.9)
Female	186 (26.1)	140 (26.8)	46 (24.1)
Age group (years)			
12 - 19	20 (2.8)	17 (3.3)	3 (1.6)
20 - 29	139 (19.5)	100 (19.2)	39 (20.4)
30 - 39	161 (22.6)	117 (22.4)	44 (23.0)
40 - 49	176 (24.7)	132 (25.3)	44 (23.0)
50 - 59	139 (19.5)	96 (18.4)	43 (22.5)
60 - 69	58 (8.1)	45 (8.6)	13 (6.8)
>70	20 (2.8)	15 (2.9)	5 (2.6)
Weight (kg)			
<50	164 (23.0)	110 (21.1)	54 (28.3)
50 - 70	475 (66.6)	347 (66.5)	128 (67.0)
>70	74 (10.4)	65 (12.5)	9 (4.7)
Total	713 (100)	522 (73.2)	191 (26.8)

[a]Group I, rifampicin once daily therapy doses ranging from 300 mg to 750 mg; [b]Group II, intermittent therapy every other day with combination blister packs of anti-TB drugs containing 600 mg of rifampicin.

Table 2. Number and proportion of TB patients treated with different doses of rifampicin in Group I.

	Patient no.	Number (%) of patients treated with		
		Standard doses	Low doses	High doses
Gender				
Male	382	94 (24.6)	285 (74.6)	3 (0.8)
Female	140	60 (42.9)	78 (55.7)	2 (1.4)
Age (years)				
12 - 19	17	10 (58.8)	7 (41.2)	0 (0)
20 - 29	100	28 (28.0)	71 (71.0)	1 (1.0)
30 - 39	117	33 (28.2)	82 (70.1)	2 (1.7)
40 - 49	132	40 (30.3)	91 (68.9)	1 (0.8)
50 - 59	96	28 (29.2)	67 (69.8)	1 (1.0)
60 - 69	45	9 (20.0)	36 (80.0)	0 (0)
≥70	15	6 (40.0)	9 (60.0)	0 (0)
Weight (kg)				
<50	110	100 (90.9)	6 (5.5)	4 (3.6)
50 - 70	347	42 (12.1)	304 (87.6)	1 (0.3)
>70	65	12 (18.5)	53 (81.5)	0 (0)
Total	522	154 (29.5)	363 (69.5)	5 (1.0)

Table 3. Number and proportion of TB patients treated with different doses of rifampicin in Group II.

	Patient no.	Number (%) of patients treated with		
		Standard doses	Low doses	High doses
Gender				
Male	145	133 (91.7)	11 (7.6)	1 (0.7)
Female	46	42 (91.3)	4 (8.7)	0 (0)
Age (years)				
12 - 19	3	3 (100.0)	0 (0)	0 (0)
20 - 29	39	35 (89.7)	3 (7.7)	1 (2.6)
30 - 39	44	40 (90.9)	4 (9.1)	0 (0)
40 - 49	44	40 (90.9)	4 (9.1)	0 (0)
50 - 59	43	42 (97.7)	1 (2.3)	0 (0)
60 - 69	13	11 (84.6)	2 (15.4)	0 (0)
≥70	5	4 (80.0)	1 (20.0)	0 (0)
Weight (kg)				
<50	54	50 (92.6)	4 (7.4)	0 (0)
50 - 70	128	118 (92.2)	9 (7.0)	1 (0.8)
>70	9	7 (77.8)	2 (22.2)	0 (0)
Total	191	175 (91.6)	15 (7.9)	1 (0.5)

Table 4. Number and proportion of TB patients in two Groups with differences in doses of rifampicin received, frequency of rifampicin-resistance and successful outcomes.

Variables	Patient no. (%)		
	Group I[a] (N = 522)	Group II[b] (N = 191)	*P* value
Low doses	363 (69.5)	15 (7.9)	<0.0001
Standard doses	154 (29.5)	175 (91.6)	<0.0001
High doses	5 (1.0)	1 (0.5)	
Rifampicin-resistance	238 (45.6)	72 (37.7)	0.0304
Successful treatment outcomes	243 (46.6)	105 (55.0)	0.0093

[a]Group I, rifampicin once daily therapy doses ranging from 300 mg to 750 mg; [b]Group II, intermittent therapy every other day with combination blister packs of anti-TB drugs containing 600 mg of rifampicin.

resistance rate of isolates collected from patients who received low doses of rifampicin (46.2% in group I and 40% in group II) was higher than those collected from patients who received standard and high doses of rifampicin (40.7% in group I and 37.5% in group II) within the same treatment group. When treatment outcomes were compared between two groups, we found that 46.6% of patients (243/522) in treatment group I and 55.0% of patients (105/191) in treatment group II were successfully treated, and the difference was statistically significant ($P < 0.0093$). The rate of successful treatment for patients in two groups whose isolates were rifampicin-resistance (24.4% in group I and 34.7% in group II) was lower than those whose isolates were rifampicin-susceptible within the same treatment group (65.1% in group I and 67.2% in group II). Results from this study indicated that the initial treatment for new TB patients with every other day combination blister packs of anti-TB drugs containing rifampicin (group II) was better than those with daily dose of bulk anti-TB drugs including rifampicin (group I) in terms of frequency of rifampicin-resistance and treatment outcomes.

4. Discussion

Results from this retrospective multicenter study confirmed that 91.6% of new TB patients treated at many TB Prevention and Treatment centers (group II), and 29.5% of those treated at specialized TB hospitals (group I) in China did receive standard doses of rifampicin. Due to less human factors were involved in the use of combination blister packs, most of TB patients in treatment group II received standard doses of rifampicin. However, the use of combination blister packs has its own drawbacks, for example, if patients forget to take the medicines, the time intervals between treatments will be extended which can affect the treatment efficacy. Fixed-dose combination (FDC) tablets containing a variety of anti-TB drugs in the proper dosages were recommended by both WHO and the International Union against Tuberculosis and Lung Diseases (IUATLD) as a means to simplify administration of drugs by reducing the number of pills patients take and decreasing the risks of incorrect prescriptions and development of drug resistance [15]. To prevent the reemergence and spread of MDR-TB, health care providers should follow established guidelines during the entire treatment period for patients with pulmonary TB.

Our results also show that 69.5% of new TB patients treated at specialized TB hospitals (group I) and 7.9% of those treated at TB prevention and treatment centers (group II) in multiple provinces of China received low doses of rifampicin. As one of the most important anti-TB drugs, rifampicin must be administered adequately in accordance with the established guidelines [2]-[5] to maximize the cure rate. If the dose is too low, the therapeutic efficacy will be reduced and the risk of drug resistance will be increased [6]. One of the possible reasons for the use of low doses of rifampicin in treatment group I was that physicians at specialized TB hospitals worried about potential adverse reactions of rifampicin, and therefore prescribed low doses of rifampicin based on their personal experience instead of following the established guidelines. We previously found that this kind of practice was quite common at many specialized TB hospitals in China [16] [17]. Similar irrational phenomenon has also occurred in other countries of the world (Kenya, Malawi, Nepal, Senegal, and Chinese Taipei) [18], which is understandable since jaundice hepatitis hepatic necrosis and fatal cases caused by rifampicin were reported in the early literature [19]. In addition, rifampicin could also cause acute allergic reactions, even though the inci-

dence is very low, and death if patients are not rescued immediately or it happens to elderly patients [20]. Among patients with liver damage caused by anti-TB drugs, 33% had no obvious symptoms [21], indicating that we need to strengthen the therapeutic drug monitoring (TDM), inform patients and their families in advance about early symptoms of adverse reactions and possible side effects, and prevent adverse reactions through team works [7].

Comparison results show that the percentage of rifampicin-resistance for clinical isolates collected from TB patients in treatment group I (45.6%) was significantly higher than those in treatment group II (37.7%), and the rate of successful treatment for patients in treatment group I (46.6%) was significantly lower than those in treatment group II (55%). Our results indicate that low doses of rifampicin used in the initial treatment of patients with TB are indeed correlated to increased frequency of rifampicin-resistance and poorer treatment outcomes, and support the idea of using higher doses of rifampicin for new TB patients to shorten the treatment duration, to reduce rifampicin-resistance, and to improve treatment outcomes.

Because this retrospective multicenter study was not a double-blind placebo-controlled clinical trial, it had some potential limitations. In addition to the difference in doses of rifampicin received by TB patients in two treatment groups, other variable factors such as administering methods for rifampicin and doses of three other first-line anti-TB drugs may also affect the frequency of rifampicin-resistance and treatment outcomes. To overcome these potential limitations, confirm the conclusions of the current study, and prove the potential benefits and unanticipated risks of using higher doses of rifampicin, multicenter randomized double-blind placebo-controlled clinical studies with more new patients with pulmonary TB in each group will need to be properly designed and conducted.

Currently, one clinical trial is planning to recruit 180 participants with active, infectious, drug-susceptible TB in Peru to evaluate the potential of higher doses of rifampicin (15 mg/kg/day and 20 mg/kg/day) to shorten treatment for tuberculosis without causing more adverse events (http://clinicaltrials.gov/show/NCT01408914). Results from a recently published study using a murine model indicated that even the standard rifampicin dosage (10 mg/kg/day) was too low, and a rifampicin dosage of 80 mg/kg/day significantly reduced therapy duration without adverse effects, which suggested that much higher doses of rifampicin might lead to a more rapid treatment response and the shortened treatment course [22]. Based on this suggestion, another clinical trial is ongoing in South Africa to determine safety, tolerability, extended early bactericidal activity and pharmaco-kinetics of even higher doses of rifampicin (10, 20, 25, 30, 35, 40, 45, 50 and 55 mg/kg/day) in adults (18 years to 65 years) with pulmonary TB (http://clinicaltrials.gov/ct2/show/NCT01392911). However, these clinical trials were not designed specifically to determine the correlation between low doses of rifampicin and frequency of rifampicin-resistance as well as treatment outcomes.

5. Conclusion

Results from our study indicate that low doses of rifampicin used for the initial treatment of new pulmonary TB patients are correlated to increased frequency of rifampicin-resistance and poorer outcomes, and the difference between two treatment groups is statistically significant. Our results also provide clinical evidence to support the idea of using higher doses of rifampicin to shorten the treatment duration, reduce the frequency of rifampicin-resistance, and improve the treatment outcomes for patients with pulmonary TB.

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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. All authors except HZ declare no conflicts of interest. HZ has shares in Z-BioMed, which is involved in infectious disease research.

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List of Abbreviations

CDC: Centers for Disease Control and Prevention
DST: Drug Susceptibility Testing
FDC: Fixed-Dose Combination
HIV: Human Immunodeficiency Virus
IUATLD: International Union against Tuberculosis and Lung Diseases
L-J: Löwenstein-Jensen
MDR: Multidrug-Resistant
Mtb: Mycobacterium Tuberculosis
TB: Tuberculosis