Full Length Research Paper

A meta analysis of the efficacy and safety of moxifloxacin in Chinese patients with multi-drug resistant pulmonary tuberculosisosis

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This study was performed to evaluate the efficacy and safety of moxifloxacin in treating Chinese patients with multi-drug resistant pulmonary tuberculosisosis (MDR-TB). Medicinal databases and review articles were screened with pre-specified criteria for randomized controlled trials that reported the effects of and adverse reactions to moxifloxacin and other antituberculosisosis drugs in treating Chinese patients with MDR-TB. The quality of included studies was critically evaluated. A total of 948 articles were found and 12 articles finally included. Heterogeneity test: Sputum negative conversion analysis (Q statistic = 9.43, \( p = 0.58, I^2 = 0\%\)), change of pulmonary tuberculosisosis cavity analysis (Q statistic = 2.93, \( p = 0.89, I^2 = 0\%\)), focus absorption analysis (Q statistic = 20.13, \( p = 0.03, I^2 = 50\%\)) and safety analysis (Q statistic = 10.98, \( p = 0.44, I^2 = 0\%\)). The results of meta-analysis showed that compared with the control group, moxifloxacin was more effective in sputum negative conversion (OR = 3.34, 95% CI: 2.37 to 4.70) and focus absorption (OR = 2.53, 95% CI: 1.55 to 4.12). Moreover, moxifloxacin was safer than control group (OR = 0.73, 95% CI: 0.55 to 0.96). Funnel-plot displayed some unsymmetrical figures, indicating there were publication biases in each analysis. The evidence currently available shows that the moxifloxacin treatment on Chinese patients with MDR-TB is useful for the sputum negative conversion and focus absorption.

Key words: Moxifloxacin, pulmonary tuberculosisosis, systemic review, meta-analysis.

INTRODUCTION

In people with latent tuberculosis (TB), a group estimated to be one-third of the world’s population, mycobacterium tuberculosis is presumed to lie in a nonreplicating (dormant) state in caseous lesions of the lungs, with little access to oxygen (Barry et al., 2009; Wayne and Hayes, 1996) or in extrapulmonary sites containing adipose tissue (Neyrolles et al., 2006). Since every year, there are mainly 500,000 reported cases of tuberculosis caused by strains of mycobacterium tuberculosis that are resistant to the key first-line drug isoniazid and rifampicin, agents that are active in multidrug-resistant tuberculosis are also needed (WHO, 2008). Additionally, the Chinese patients with MDR-TB were second in the world (WHO, 2006). The development of novel drug regimens for MDR-TB is an urgent global health priority (Young et al., 2006). Moxifloxacin is a fluoroquinolone that has potent in-vitro activity against MDR-TB (Ji et al., 1998; Gillespie and Billington, 1999). Earlier studies of moxifloxacin in murine models of tuberculosis showed that it had good bactericidal activity that was additive to isoniazid (Miyazaki et al., 1999; Lounis et al., 2001). Though there are several clinic studies (Burman et al., 2006; Conde et al., 2009; Dorman et al., 2009) about moxifloxacin in treatment of MDR-TB, the conclusions of which are not credible because of small sample size and lacks of systemic evaluation of methodologic quality.

In our present work, we make a systemic review about clinical random control trials (RCTs) focused on moxifloxacin in treatment of Chinese patients with MDR-TB in order to obtain the best evidence about the...
efficacy and safety of moxifloxacin in treating Chinese patients with MDR-TB.

METHODS

Search sources and strategy
The search strategy was made according to working handbook 4.2.7 from the Cochrane collaboration (Sackett et al., 2002). We systematically searched MEDLINE (1991 to September 2011), EMBase (1991 to September 2011), CBMdisc (1991 to September 2011) and CNKI (1994 to September 2011) for randomized trials examining the efficacy and safety of moxifloxacin on MDR-TB patients. In addition, we conducted a manual search of abstracts from selected conferences and we also searched by hand the bibliographies of all relevant trials. The following search criterion was used: (“pulmonary tuberculosis”, “pneumonophthisis” or “MDR-TB”) and (“moxifloxacin”, “avelox”, “moxifloxacinum”, “moxifloxaciné” or “moxifloxacino”) and language was limited to English or Chinese.

Study selection
Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies were used for appropriateness before retrieval of the full articles. The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (a) study design-RCTs; (b) population- Chinese patients with MDR-TB (WHO-ISH Tuberculosisis Guidelines Committee, 2003; Chinese guidebook on prevention and treatment of tuberculosis, 2002); (c) intervention: moxifloxacin versus other active antituberculosis agents such as levofloxacin and sparfloxacin; (d) outcome variable: sputum negative conversion rate, change of tuberculosis cavity rate, focus absorption rate and adverse reaction rate.

Data extraction
From each study, the following information was abstracted: author, year of publication, study design, characteristics of the population, simple size, treatment proposal, time of the therapy, sputum negative conversion rate, change of tuberculosis cavity rate, focus absorption rate and adverse reactions (ADRs) rate.

Assessment of study quality
Quality of the included studies was assessed based on a well-established, validated scale developed by Jadad et al. (1996). A Jadad score was calculated using the following 7 items: (i) Was the study described as a random trial? (ii) Was the randomization scheme described as appropriate? (iii) Was the study described as double-blind? (iv) Was the method of double blinding appropriate? (Were both the patient and the assessor appropriately blinded?) (v) Was there a description of dropouts and withdrawals? (vi) Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate; (vii) Deduct one point if the study was described as double blind but the method of blinding was inappropriate. The first five items were indications of good quality and each counted as one point towards an overall quality score. The final two items indicated poor quality and a point were subtracted for each if its criteria were not met.

The range of possible scores was 0 to 5 (0 being weakest and 5 being strongest). Any study with a Jadad score < 3/5 was considered to be of poor quality and was excluded.

RESULTS

Study characteristics
There were 948 articles relevant to the search term and 12 articles (Chen et al., 2009, 2011; Huang et al., 2011; Liang et al., 2011; Tang, 2008; Wang and Wang, 2009; Wang and Gao, 2010; Xiao et al., 2006; Zhang et al., 2007a, b; Zhao, 2007) involving 924 patients with MDR-TB (group moxifloxacin: 509 patients, group control: 415 patients) were included in this meta-analysis. Ages, sex ratio and initial blood pressure were similar in each group, respectively. The flow chart for the selection of RCTs to be included in our analysis is shown in Figure 1. The characteristics of the included trials were showed in Table 1.

Statistical analysis
For dichotomous outcomes, we calculated a pooled odds ratio (OR) and 95% confidence interval (CI). The OR was defined as the odds of an outcome in those who received moxifloxacin compared with the odds in those who received other active agents. The ORs of different RCTs were combined by using the random effects model as previously described (Der and Laird, 1986), if true between-study heterogeneity exists or else using Mantel and Haenszel fixed-effects model instead (Mantel and Haenszel, 1959). Intertrial statistical heterogeneity was explored using the Cochran Q test with calculated $I^2$, indicating the percentage of the total variability in effect estimates among trials that are due to heterogeneity rather than to chance (Higgins et al., 2003). $I^2$ values of 50% or more indicate a substantial level of heterogeneity. We evaluated the presence of publication bias by means of visual inspection of the funnel plot (whether it was symmetrical or not). To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by excluding those studies with low quality and then rerunning the analysis to assess the change in ORs.

All $p$ values were two-sided with statistical significance set at an $\alpha$ level of 0.05. We followed the “quality of reporting meta-analysis guidelines” for reporting and discussing these meta-analytical results (Moher et al., 1999). All the statistical analysis was carried out by the Cochrane collaboration’s RevMan 5.0 software.

Heterogeneity test
We choose fixed-effect model to make meta-analysis because there were no significant heterogeneities among
Meta-analysis of sputum negative conversion

Moxifloxacin and group control were recorded in all the 12 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin andsparfloxacin. The results of meta-analysis (OR = 3.34 95% CI: 2.37 to 4.70) confessed that moxifloxacin is more effective than control group in sputum negative conversion of Chinese patients with MDR-TB (Figure 2).

Meta-analysis of change of pulmonary tuberculosis cavity

Moxifloxacin and group control were recorded in all the 8 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin. The results of meta-analysis (OR = 1.38 95% CI: 0.99 to 1.90) confessed that there were no significant differences in changing cavity between...
Table 1. Characteristics of the 12 randomized clinical studies included in this meta-analysis.

<table>
<thead>
<tr>
<th>Author and Jaded score</th>
<th>Year</th>
<th>Duration (months)</th>
<th>Treatment Protocol (T/C)</th>
<th>Sample size (T/C)</th>
<th>Sputum negative conversion rate (%)</th>
<th>Change of tuberculosis cavity rate (%)</th>
<th>Focus absorption rate (%)</th>
<th>Adverse reaction rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xiao et al. Score = 3</td>
<td>2006</td>
<td>21</td>
<td>T: M+CcrEPThZ C: V+CcrEPThZ</td>
<td>T: 35 C: 30</td>
<td>77.1 NA</td>
<td>NA</td>
<td>11.4</td>
<td>33.3</td>
</tr>
<tr>
<td>Zhang et al. Score = 3</td>
<td>2007</td>
<td>12</td>
<td>T: M+ADEL C: V+ADEL</td>
<td>T: 62 C: 64</td>
<td>93.5 86</td>
<td>61.3 53</td>
<td>80.6 76.6</td>
<td>38.7 53.1</td>
</tr>
<tr>
<td>Zhang et al. Score = 3</td>
<td>2007</td>
<td>12</td>
<td>T: M+DL C: V+DL</td>
<td>T: 31 C: 30</td>
<td>90.3 76.7</td>
<td>48.4 46.7</td>
<td>64.5 50</td>
<td>22.9 26.5</td>
</tr>
<tr>
<td>Zhang et al. Score = 3</td>
<td>2007</td>
<td>12</td>
<td>T: M+ADLE C: Sp+ADLE</td>
<td>T: 36 C: 35</td>
<td>91.7 82.9</td>
<td>84.8 78.1</td>
<td>88.9 80</td>
<td>15.4 35.0</td>
</tr>
<tr>
<td>Zhao et al. Score = 2</td>
<td>2007</td>
<td>12</td>
<td>T: M+CDLTh C: V+CDLTh</td>
<td>T: 31 C: 31</td>
<td>87.1 74.2</td>
<td>NA</td>
<td>90.3 77.4</td>
<td>12.9 16.1</td>
</tr>
<tr>
<td>Tang et al. Score = 2</td>
<td>2008</td>
<td>12</td>
<td>T: M+DELTh C: V+DELTh</td>
<td>T: 62 C: 64</td>
<td>88.7 75</td>
<td>NA</td>
<td>91.9 75</td>
<td>16.1 18.8</td>
</tr>
<tr>
<td>Chen et al. Score = 2</td>
<td>2009</td>
<td>18</td>
<td>T: M+AmCDCrPas C: V+AmCDCrPas</td>
<td>T: 43 C: 42</td>
<td>95.3 71.4</td>
<td>97.7 85.7</td>
<td>97.7 85.7</td>
<td>32.6 31</td>
</tr>
<tr>
<td>Wang et al. Score = 3</td>
<td>2009</td>
<td>18</td>
<td>T: M+AEZL C: V+AEZL</td>
<td>T: 96 C: 96</td>
<td>93.8 91.7</td>
<td>56.3 51</td>
<td>82.2 85.4</td>
<td>23.9 28.1</td>
</tr>
<tr>
<td>Wang et al. Score = 3</td>
<td>2010</td>
<td>21</td>
<td>T: M+ADLThZ C: ADLThZ</td>
<td>T: 46 C: 47</td>
<td>87 59.6</td>
<td>NA</td>
<td>93.5 55.3</td>
<td>29.2 26.5</td>
</tr>
<tr>
<td>Chen et al. Score = 4</td>
<td>2011</td>
<td>12</td>
<td>T: M+DEThZ C: V+DEThZ</td>
<td>T: 24 C: 27</td>
<td>91.6 74.1</td>
<td>66.6 55.6</td>
<td>83.3 66.7</td>
<td>23.7 22.8</td>
</tr>
<tr>
<td>Huang et al. Score = 3</td>
<td>2011</td>
<td>21</td>
<td>T: M+ALPZ C: V+ALPZ</td>
<td>T: 63 C: 63</td>
<td>92.1 57.1</td>
<td>80 71.1</td>
<td>79.4 46</td>
<td>4.5 4.5</td>
</tr>
<tr>
<td>Liang et al. Score = 3</td>
<td>2011</td>
<td>18</td>
<td>T: M+ALPPasTh Z</td>
<td>T: 35</td>
<td>82.9 81.6</td>
<td>91.4 26.1</td>
<td>26.1</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Contd.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2009</td>
<td>41</td>
<td>43</td>
<td>30</td>
<td>3.7% 8.20 [1.71, 39.39]</td>
<td></td>
</tr>
<tr>
<td>Chen 2011</td>
<td>22</td>
<td>24</td>
<td>20</td>
<td>4.1% 3.85 [0.71, 20.74]</td>
<td></td>
</tr>
<tr>
<td>Huang 2011</td>
<td>58</td>
<td>63</td>
<td>36</td>
<td>7.4% 8.70 [3.07, 24.64]</td>
<td></td>
</tr>
<tr>
<td>Liang 2011</td>
<td>29</td>
<td>35</td>
<td>18</td>
<td>8.6% 3.22 [1.03, 10.10]</td>
<td></td>
</tr>
<tr>
<td>Tang 2008</td>
<td>55</td>
<td>62</td>
<td>48</td>
<td>13.8% 2.62 [0.99, 6.90]</td>
<td></td>
</tr>
<tr>
<td>Wang 2009</td>
<td>90</td>
<td>96</td>
<td>88</td>
<td>14.3% 1.36 [0.45, 4.09]</td>
<td></td>
</tr>
<tr>
<td>Wang 2010</td>
<td>40</td>
<td>46</td>
<td>27</td>
<td>9.0% 4.94 [1.75, 13.90]</td>
<td></td>
</tr>
<tr>
<td>Xiao 2006</td>
<td>27</td>
<td>35</td>
<td>19</td>
<td>12.1% 1.95 [0.66, 5.77]</td>
<td></td>
</tr>
<tr>
<td>Zhang 2007a</td>
<td>58</td>
<td>62</td>
<td>55</td>
<td>9.1% 2.37 [0.69, 8.15]</td>
<td></td>
</tr>
<tr>
<td>Zhang 2007b</td>
<td>28</td>
<td>31</td>
<td>22</td>
<td>5.6% 3.39 [0.80, 14.32]</td>
<td></td>
</tr>
<tr>
<td>Zhang 2007c</td>
<td>33</td>
<td>36</td>
<td>29</td>
<td>6.4% 2.28 [0.52, 9.93]</td>
<td></td>
</tr>
<tr>
<td>Zhao 2007</td>
<td>28</td>
<td>31</td>
<td>23</td>
<td>5.9% 2.84 [0.66, 12.24]</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Sputum negative conversion between the treatment and control groups.
## Meta-analysis of focus absorption

Moxifloxacin and control group were recorded in all the 11 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin. The results of meta-analysis (OR = 2.53, 95% CI: 1.55 to 4.12) confessed that moxifloxacin is more effective than control group in focus absorption in treating Chinese patients with MDR-TB (Figure 4).

### Moxifloxacin and control group

The active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin.
group were recorded in all the 12 trials finally included. Main adverse reactions of moxifloxacin group were gastrointestinal symptoms and liver injuries. The results of meta-analysis (OR = 0.73 95% CI: 0.55 to 0.96) confessed that moxifloxacin is safer than control group in treating Chinese patients with MDR-TB (Figure 5).

**Publication bias**

An analysis of publication bias was conducted. The funnel plots to assess publication bias are shown in Figure 6. The shape of the funnel plots show some asymmetries in all studies included in the meta-analysis. There exist some publication biases since the funnel plots were unsymmetrical based on a visual analysis (Figure 6). However, the publication biases might be relevant to some methodological insufficiencies: (1) Randomization method may not be rigorous because the specific program of randomization was inferred in only one literature. (2) Selection bias may exist for allocation concealment was not described in all of these articles included. (3) Selection bias, measuring bias and implementation bias may exist because 3 studies did not describe whether blind method was used or not.

**DISCUSSION**

A total of 12 literatures were finally included in this systemic review. All these articles including a sample size of 948 totally were RCTs. Jadad score in 9 out of the 12 articles were more than three points. All the trials included in this meta-analysis mentioned the term ‘random’, but the detail method was illuminated in 1 article only. Obviously, the included trials were lack of well-designed randomizations. A well-designed randomized controlled trial requires a thorough understanding of randomization so that better results could be achieved. Randomization includes three important steps, namely: sequence generation, allocation concealment and randomization implementation. Sequence generation is a method used to generate the random allocation sequence including details of any restriction. Allocation concealment is to implement the random allocation sequence. Randomization implementation is to generate the allocation sequence. Well-men designed randomized controlled trials are required to evaluate moxifloxacin treatment versus routine treatment in Chinese population. It was suggested that we should be careful for randomization. Moxifloxacin, a novel fluoroquinolone that has potent *in-vitro* activity against MDR-TB. Compared with other fluoroquinolones, moxifloxacin has the characteristics of strong bactericidal activity that was additive to isoniazid.

The results of this systemic review showed that moxifloxacin were more effective than control group in sputum negative conversion and focus absorption in treating Chinese patients with MDR-TB. Thus, we can conclude that moxifloxacin has stronger effect compared with other active antituberculosis agents. The adverse
reactions including gastrointestinal symptoms and liver injury mainly of moxifloxacin in treating MDR-TB referred in this study were less likely to happen. The results of this systemic review showed that moxifloxacin has less ADRs than control group in treating Chinese patients with MDR-TB. Therefore, we could conclude that moxifloxacin was safer compared with other active antituberculosis agents.

We urgently hope the high-quality, double-blinded, multi-centered RCTs will be carried out in future to further confirm its efficacy and safety.

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REFERENCES


