

## CAT Assignment (Critically Appraised Topic)

Title: The Efficacy of Moxifloxacin in the Treatment of Multidrug-resistant Tuberculosis

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<p>1. Reference: Koh WJ, Lee SH, Kang YA, <i>et al.</i> Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. <i>Am J Respir Crit Care Med.</i> 2013; 188(7): 858-64.</p>
<p>2. Clinical Question: What is the efficacy of the use of moxifloxacin in the treatment of multidrug-resistant mycobacterium tuberculosis (MDR-TB) compared to other MDR-TB therapies?</p> <p>PICO Parts:</p> <p>P – adult patients (18 years or older) diagnosed with MDR-TB</p> <p>I – moxifloxacin</p> <p>C – other medications used to treat MDR-TB</p> <p>O – Moxifloxacin more effectively treats MDR-TB than other antitubercular drugs.</p>
<p>3. Search Strategy</p> <p>a. Database(s) searched: Pubmed</p> <p>b. Keyword Search Terms used: moxifloxacin, drug resistant tuberculosis</p> <p>c. MeSH Search Terms used: "Tuberculosis, Multidrug-Resistant/drug therapy"[MAJR]</p> <p>d. Limits used: Clinical Trial, 5 years</p> <p>e. Complete search strategy: (("moxifloxacin"[Supplementary Concept] OR "moxifloxacin"[All Fields]) AND ("tuberculosis, multidrug-resistant"[MeSH Terms] OR ("tuberculosis"[All Fields] AND "multidrug-resistant"[All Fields]) OR "multidrug-resistant tuberculosis"[All Fields] OR ("drug"[All Fields] AND "resistant"[All Fields] AND "tuberculosis"[All Fields]) OR "drug resistant tuberculosis"[All Fields])) AND "Tuberculosis, Multidrug-Resistant/drug therapy"[MAJR] AND (Clinical Trial[ptyp] AND "2011/03/27"[PDat] : "2016/03/24"[PDat])</p>
<p>4. Methods Description (setting, population, sample size, study design)</p>

This study was a prospective, multicenter, stratified, randomized, open-label clinical trial. Participants for this trial were selected from 19 different institutions across South Korea. Inclusion criteria for participation included

- Positive sputum culture for pulmonary tuberculosis with MDR-TB strains.
- MDR-TB strains were sensitive to levofloxacin (LFX) and moxifloxacin (MXF) based on *in vitro* drug susceptibility testing.

Patients with MDR-TB strains resistant to ofloxacin were also enrolled in the study if the strains were LFX and MXF sensitive.

Participants selected for this study were in the age range of 20 to 75 years. Initially, a total of 182 patients were recruited to the trials, and they were randomly assigned to the LFX (90) or MXF (92) group and screened for the aforementioned inclusion criteria. Over the course of the twelve-week trial, a total of 17 patients in the LFX group and 18 20 participants either did not meet the inclusion criteria or were lost to attrition. Two participants in the LFX group were changed to the MFX group due to adverse drug reactions to LFX. The final totals for each treatment group were 73 (LFX) and 74 (MFX).

Patients were treated for 12 weeks with either MFX or LFX. Each month, sputum samples were collected from participants and cultured to test for presence of MDR-TB strains.

#### 5. Methods Interpretation (Validity):

- a. Was there an independent “blind” comparison with a reference standard?
  - i. No. This was a prospective study that was stratified, randomized, and open-label. In open-label trials both the researchers and the participants are aware of which treatment is being administered. No reference standard was used for this study; however, moxifloxacin and levofloxacin were compared to each other as they are the most commonly used fluoroquinolones in the treatment of MDR-TB. Levofloxacin is the favored fluoroquinolone treatment according to the MDR-TB treatment guidelines established by the World Health Organization.
- b. Did the sample include an appropriate spectrum of patients to whom the diagnostic/screening test will be applied in clinical practice?
  - i. The sample included an appropriate spectrum of patients to which the diagnostic/screening test was applied. Patients who presented with multidrug-resistant tuberculosis (resistant to rifampin and isoniazid) that showed *in vitro* sensitivity to both levofloxacin and moxifloxacin were enrolled in this study. As the study was conducted across 19 institutions, there was significant heterogeneity across subjects; of note, all of the institutions were in South Korea, so that may introduce some level of selection bias. There is also a possibility that there is a meaningful difference in the patients or the strains such that this data may not directly apply to a population in another country such as the United States with a different racial profile or strain of MDR-TB.

- c. Did the results of the diagnostic/screening test being evaluated influence the decision to perform the reference standard?
  - i. No. All patients in this study received a baseline treatment regimen in addition to the therapies being studied (LFX and MFX). The results of the diagnostic/screening test did not influence group assignment.
- d. Were the methods for performing the diagnostic/screening test described in sufficient detail to permit replication?
  - i. Yes, the patients were included in the study based on a positive sputum culture for acid-fast bacteria with subsequent susceptibility tests that revealed resistance to rifampin and isoniazid. Patients were also enrolled if their sputum smears were positive for acid-fast bacilli coupled with a positive rapid test for isoniazid and rifampin resistance. These were later excluded if their sputum cultures were negative or if the isolated MDR-TB were found to be resistant to levofloxacin and/or moxifloxacin. Exclusion criteria included: suspected HIV/AIDS; history of arrhythmia; allergy to study drugs; use of drugs containing metal ions such as antacids or iron-containing drugs; use of warfarin, phenytoin, theophylline, or probenecid; abnormal renal and/or hepatic lab results; pregnancy; breastfeeding. Women with childbearing potential were required to use birth control.

#### 6. Results:

After 3 months, patients from both treatment groups (LFX and MXF) were tested for conversion to negative sputum cultures. The results indicated that 88.3% (68 out of 77) patients in the LFX group and 90.5% (67 out of 74) patients in the MXF group showed conversion to negative sputum cultures with a 95% confidence interval of 0.27-2.20. The confidence interval indicates that these results are not significant because the range includes one, indicating that moxifloxacin is not superior to levofloxacin when treating MDR-TB patients. The authors indicated that research is limited in terms of a unified indicator for determining MDR-TB. The primary outcome for this study was sputum culture conversion at three months rather than treatment success or relapse rate. There is no evidence that sputum culture conversion at three months could predict long-term outcomes of MDR-TB.

#### 7. Translational applications (How does this study apply to your patients? Be specific regarding a T1-T4 level):

- This study was a phase III clinical trial; therefore, it is categorized as level T2 on the Clinical and Translational Research Spectrum. T2 level studies have the potential to influence an individual clinic's decision to incorporate new therapies for specific disease into practice. There is potential for this study to influence clinics to consider the addition of moxifloxacin as an option for treatment in patients diagnosed with MDR-TB.
- Based on the results of this study, the likelihood that clinics will choose moxifloxacin over levofloxacin when treating patients with MDR-TB is low. The

percent of patients who convert to negative sputum culture in clinics that elect to use moxifloxacin would be comparable to clinics that elect to use levofloxacin; therefore, moxifloxacin does not offer a better alternative to the WHO preferred levofloxacin.

- Before applying to our patient population, we would recommend replicating the study in the U.S. because of possible differences in the characteristics of the populations studied in this trial from those we see in our clinics daily. Geographical and ethnic differences must be taken into consideration when selecting medical therapies. Follow-up studies should include treatment success and relapse rates to further evaluate treatment efficacy.