Impact of Standard or Increased Moxifloxacin Dose Among MDR-TB Patients in Mumbai with Low-Level Resistance

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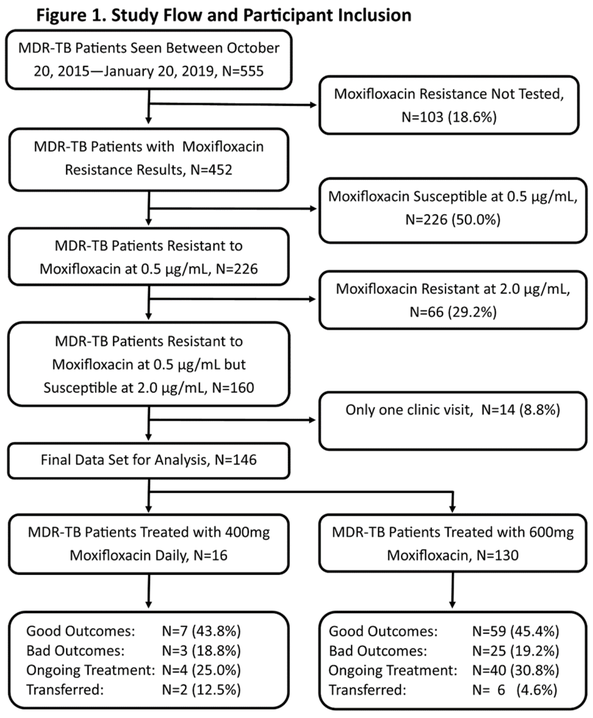
BACKGROUND

- Tuberculosis (TB) is the #1 infectious disease killer worldwide, and 26% of cases occur in India.
- The city of Mumbai is particularly affected, with 12% of India's Multidrug-Resistant TB (MDR-TB, TB resistant to isoniazid and rifampin).
- Rreported rates of resistance to both isoniazid and rifampin (multidrug resistant tuberculosis, "MDR-TB") are rising globally.
- The expansion of shorter, injectable-sparing MDR-TB regimens has reinforced the importance of fluoroquinolone treatment for MDR-TB.
- Some labs test moxifloxacin at multiple concentrations to identify low-level resistance that could be treated with higher moxifloxacin doses.
- To assess the impact of moxifloxacin 600mg daily ("high-dose moxifloxacin") vs. standard moxifloxacin 400mg daily ("low-dose moxifloxacin"), we reviewed outcomes of MDR-TB patients with low-level moxifloxacin resistance.

METHODS

- MDR-TB patients seeking care at the Outpatient Chest Clinic at PD Hinduja National Hospital and Medical Research Centre were consented for prospective observational cohort. TB history, prescriptions, labs, and imaging were recorded on paper CRFs, entered into an Access database., and cleaned and analyzed in R.
- Susceptibility to moxifloxacin was tested in MGIT at 0.5µg/mL and 2.0µg/mL. Participants resistant at 0.5µg/mL but susceptible at 2.0µg/mL with multiple clinic visits were analyzed by moxifloxacin dose.
- The primary outcome of interest was "Good Outcome" (defined as 2 years of treatment completed or cured) vs. "Bad outcome" (composite of death, loss to follow-up, or culture reversion).
- Secondary outcomes included weight gain, change in chest X-ray score (% of lung affected + 40 in the presence of a cavity), culture conversion, and time to smear and culture conversion.
- Differences in proportions were calculated by χ^2 tests and Wilcoxon rank sum tests. Odds were calculated by univariate regressions including age, sex, site of disease, X-ray score, presence of cavitary or bilateral lung disease, other drug resistance, other drug treatments, or lung resection
- Kaplan Meier curves were used to calculate time to smear and culture conversion.

Figure 1. Study Flow and Participant Inclusion



RESULTS: Participant Characteristics

- 555 participants enrolled from October 20 2015—January 20, 2019, 146 were included in this analysis.

Participant Characteristics	400 MG DAILY	600MG DAILY	ALL PATIENTS	P-VALUE[2]
DEMOGRAPHICS	**N (%)**	**N (%)**	**N (%)**	
AGE[1]	23.5 (19.8-35.3)	29 (22.0-37.0)	28 (22.0-36.0)	0.130
FEMALE SEX	14 (87.5)	73 (56.2)	87 (59.6)	0.032
PULMONARY DISEASE ONLY	12 (75.0)	107 (82.3)	119 (81.5)	0.712
HISTORY OF PRIOR TB	4 (25.0)	33 (25.4)	37 (25.3)	1.000
BODY MASS INDEX (BMI)[1]	18.9 (16.1-20.9)	20.6 (16.5-23.7)	20.3 (16.5-23.6)	0.356
HIV POSITIVE	0 (0.0)	0 (0.0)	0 (0.0)	0.356
DIABETIC	0 (0.0)	14 (10.8)	14 (9.6)	1.000
MICROBIOLOGY				
XDR TB	3 (18.8)	43 (33.1)	46 (31.5)	0.379
SMEAR POSITIVE	11 (68.8)	104 (80.0)	115 (78.8)	0.475
CULTURE POSITIVE	16 (100.0)	125 (96.2)	141 (96.6)	1.000
ADDITIONAL TREATMENT				
TREATED WITH CLOFAZIMINE	8 (50.0)	94 (72.3)	102 (69.9)	1.000
TREATED WITH LINEZOLID	2 (12.5)	88 (67.7)	90 (61.6)	<0.001
TREATED WITH PAS	9 (56.2)	100 (76.9)	109 (74.7)	1.000
TREATED WITH CYCLOSERINE	6 (37.5)	89 (68.5)	95 (65.1)	0.277
TREATED WITH ETHIONAMIDE	5 (31.2)	63 (48.5)	68 (46.6)	0.936
TREATED WITH KANAMYCIN	6 (37.5)	61 (46.9)	67 (45.9)	1.000
TREATED WITH CAPREOMYCIN	3 (18.8)	48 (36.9)	51 (34.9)	0.633
TREATED WITH PYRAZINAMIDE	2 (12.5)	52 (40.0)	54 (37.0)	0.192
TREATED WITH ETHAMBUTOL	1 (6.2)	44 (33.8)	45 (30.8)	0.130
TREATED WITH LUNG RESECTION	1 (6.2)	9 (6.9)	10 (6.8)	1.000
TOTAL IN STUDY GROUP	16 (100.0)	130 (100.0)	146 (100.0)	–

[1]Median and Inter-Quartile Range (IQR)
[2]P-values derived from χ^2 tests for categorical and Wilcoxon rank sum tests for continuous variables

- More patients given low dose moxifloxacin were female, and more participants given high dose moxifloxacin treated with linezolid. No other significant differences were identified between groups.

RESULTS: Univariate Analysis of Outcomes

Differences in Outcomes by Dose of Moxifloxacin

Participant Characteristics	400 MG DAILY	600MG DAILY	ALL PATIENTS	P-VALUE[2]
GOOD OUTCOMES	**N (%)**	**N (%)**	**N (%)**	
CURED OR COMPLETED TREATMENT	7 (43.8)	59 (45.4)	66 (45.2)	1.000
COMPLETED TREATMENT	3 (18.8)	15 (11.5)	18 (12.3)	0.671
SMEAR CONVERTED	6 (37.5)	50 (38.5)	56 (38.4)	0.909
CULTURE CONVERTED	7 (43.8)	72 (55.4)	79 (54.1)	0.431
BAD OUTCOMES				
DIED	1 (6.2)	5 (3.8)	6 (4.1)	1.000
LOST TO FOLLOWUP	2 (12.5)	19 (14.6)	21 (14.4)	1.000
TREATMENT FAILURE	1 (6.2)	23 (17.7)	24 (16.4)	0.557
SECONDARY OUTCOMES				
WEIGHT GAIN (KG)[1]	2.0 (0.0-6.0)	2.5 (-0.8-7.0)	2.0 (-0.3-7.0)	0.982
BMI CHANGE (KG/M^2)[1]	0.8 (0.0-2.0)	0.9 (-0.4-2.9)	0.8 (-0.3-2.8)	0.966
INCREASE IN CHEST XRAY SCORE[1]	10.0 (-7.5-45.3)	15 (0.0-50.0)	15 (0.0-50.0)	0.324
TOTAL TIME TO SMEAR CONVERSION (MONTHS)[1]	7.7 (5.7-10.8)	7.4 (4.4-16.0)	7.6 (4.7-15.5)	0.896
TOTAL TIME TO CULTURE CONVERSION (MONTHS)[1]	5.8 (4.9-7.7)	6.2 (3.5-11.7)	6.1 (3.7-11.4)	0.868

[1]Median and Inter-Quartile Range (IQR)
[2]P-values derived from χ^2 tests for categorical and Wilcoxon rank sum tests for continuous variables

RESULTS: Multivariate Analysis of Outcomes

Multivariate Odds Ratios (OR) of Treatment Outcomes, By Outcome of Interest

Variable	OR (95% CI)	P-VALUE
Good Outcome		
(Intercept)	-7.4 (-9.0 – -6.0)	<0.001
High Dose Moxifloxacin	-0.3 (-1.3 – 1.1)	0.596
Initial BMI	<0.1 (0.0 – 0.1)	0.138
Died		
(Intercept)	-8.1 (-12.8 – -4.8)	<0.001
High Dose Moxifloxacin	-2.7 (-5.8 – 0.7)	0.076
XDR-TB	2.1 (-0.4 – 5.5)	0.134
Initial Chest X-ray Score	<0.1 (0.0 – 0.1)	**0.039**
Duration of Moxifloxacin	<0.1 (0.0 – <0.0)	**0.032**
Treatment Failure		
(Intercept)	-5.8 (-8.8 – -3.9)	<0.001
High Dose Moxifloxacin	0.5 (-1.1 – 3.4)	0.660
Female Sex	-0.9 (-1.9 – -0.1)	**0.038**

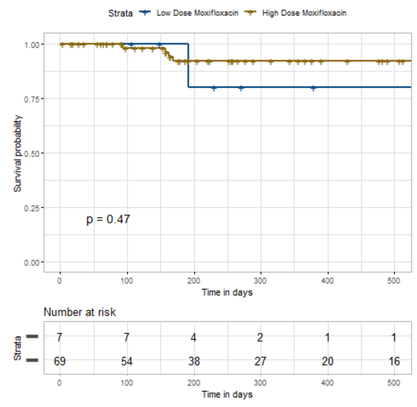
Variable	OR (95% CI)	P-VALUE
Culture Conversion		
(Intercept)	-7 (-8.4 – -5.7)	<0.001
High Dose Moxifloxacin	0.1 (-0.7 –1.2)	0.799
Pulmonary TB Only	1.1 (0.3 – 2.1)	**0.020**
Duration of Follow-up	<0.1 (0.0 – <0.0)	**0.001**
Change in Chest X-ray Score		
(Intercept)	-11.2 (-38.1 –15.8)	0.419
High Dose Moxifloxacin	11.8 (-8.7 –32.3)	0.263
Female Sex	-10.4 (-22.4 –1.7)	0.096
Delay in Starting Treatment (Months)	-0.6 (-1.3 – 0.1)	0.117
Initial Chest X-ray Score	0.5 (0.3 – 0.6)	**<0.001**
Duration of Follow-up	<0.0 (0.0 – 0.1)	**<0.001**
Ethionamide Treatment	-11.1 (-22.3 – 0.2)	0.059
Capreomycin Treatment	-11.9 (-25.0 – 1.1)	0.076
Weight Increase in Kg		
(Intercept)	-0.5 (-14 – 12.9)	0.940
High Dose Moxifloxacin	-0.9 (-14.4 – 12.6)	0.900
Diabetic	-5.8 (-11.1 – -0.5)	**0.042**
Duration of Follow-up	<0.1 (0.0 – <0.0)	**0.002**

- **High dose moxifloxacin was not significantly associated with odds of any of the clinical outcomes tested in multivariate stepwise regression models**
- Odds of death was associated with initial chest X-ray score and duration of treatment, though the contribution was minimal. Odds of culture conversion and change in chest Xray score were both associated with pulmonary disease and duration of follow-up. Odds of weight gain were associated with diabetes and duration of follow-up.

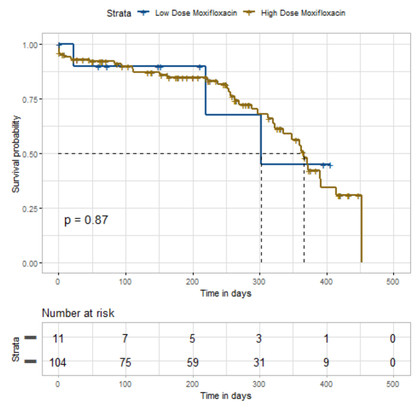
RESULTS: Time to Event

Figure 2. Time to Smear and Culture Conversion with Moxifloxacin Treatment, by Dose

Time to Culture Conversion



Time to Smear Conversion



- High dose moxifloxacin treatment was not associated with either faster smear or culture conversion

CONCLUSIONS

- Treatment of MDR-TB patients with low-level moxifloxacin resistance (susceptible at concentrations between 0.5—2.0 µg/mL) with moxifloxacin 600mg daily was not associated with improved outcomes compared to treatment with moxifloxacin 400mg daily.
- Though the overall cohort was large, interpretation of results was limited by low numbers of participants treated with moxifloxacin 400mg daily and low rates of bad outcomes.
- Future studies will compare the use of moxifloxacin 600mg to non-moxifloxacin-based treatment regimens among participants with low-level resistance.

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