Fluoroquinolones in the treatment of MDR-TB: Experience from three US TB treatment centers

Mohammad H. Al-Shaer, Wael A. Alghamdi, Guohua An, Abdullah Alsultan, Yosra Alkabab, Sayera Banu, Carolina De Miranda Silva, Amirhossein Hajihosseini, Maia Kipiani, Farzaneh Maleki, George Drusano, Stephan Schmidt, Scott Heysell, Russell R. Kempker, Peter Cegielski, Charles A. Peloquin

Background

- Increasing burden of MDR and XDR-TB
- Fluoroquinolones (FQs) are essential part of MDR-TB regimens
- Bactericidal activity
- Initially, ofloxacin (OFL) and ciprofloxacin (CIP) were used, then levofloxacin (LVX) and moxifloxacin (MOX).
- Recently, LVX/MOX moved up to group A for treating MDR-TB.

- We aim to present accumulated experience with FQs in the treatment of MDR-TB.

Methods

- Multi-center, retrospective study
- A.G. Holley Hospital (AGH), Texas Center for Infectious Diseases (TCID), and University of Texas Health Science at Tyler
- Inclusion: patients admitted between 1984 and 2015, MDR-TB, and received a FQ for ≥ 28 days.

Methods

- Data collected: demographics, sputum cultures and susceptibility, duration of treatment, treatment outcomes, and FQ serum concentrations

- Treatment outcomes:
  - *Cured*: if there was at least 1 negative culture after 6 months of therapy, with no subsequent positive cultures.
  - *Failed*: a positive culture after 6 months of treatment or death.

Methods

- Culture conversion: two consecutive negative cultures with no positive culture thereafter.
- A time-to-event (TTE) analysis was conducted to compare the time to culture conversion among patients treated with FQs.

  - Time: the number of weeks from the start of treatment to culture conversion.
  - Censoring: if the last culture / smear was positive in the medical charts
  - Exclusion: patients who had negative cultures / smears from the start

Methods

- Population PK models were established using rich PK data from other studies, along with sparse PK data from current study.

- Empirical Bayes Estimates (EBEs) for C_{max} and $AUC_{0\text{-}24}$ were then obtained.

Methods

- For PK/PD analysis, ECOFF values in liquid medium of **1.0** mg/L for LVX and **0.25** mg/L for MOX as the MIC.

- *Unbound* drug fraction was estimated at 70% LVX and 60% MOX.

- Software: JMP Pro v13.0, SAS (statistical analysis), Monolix v2018R1, Lixoft (PK modeling).

Results

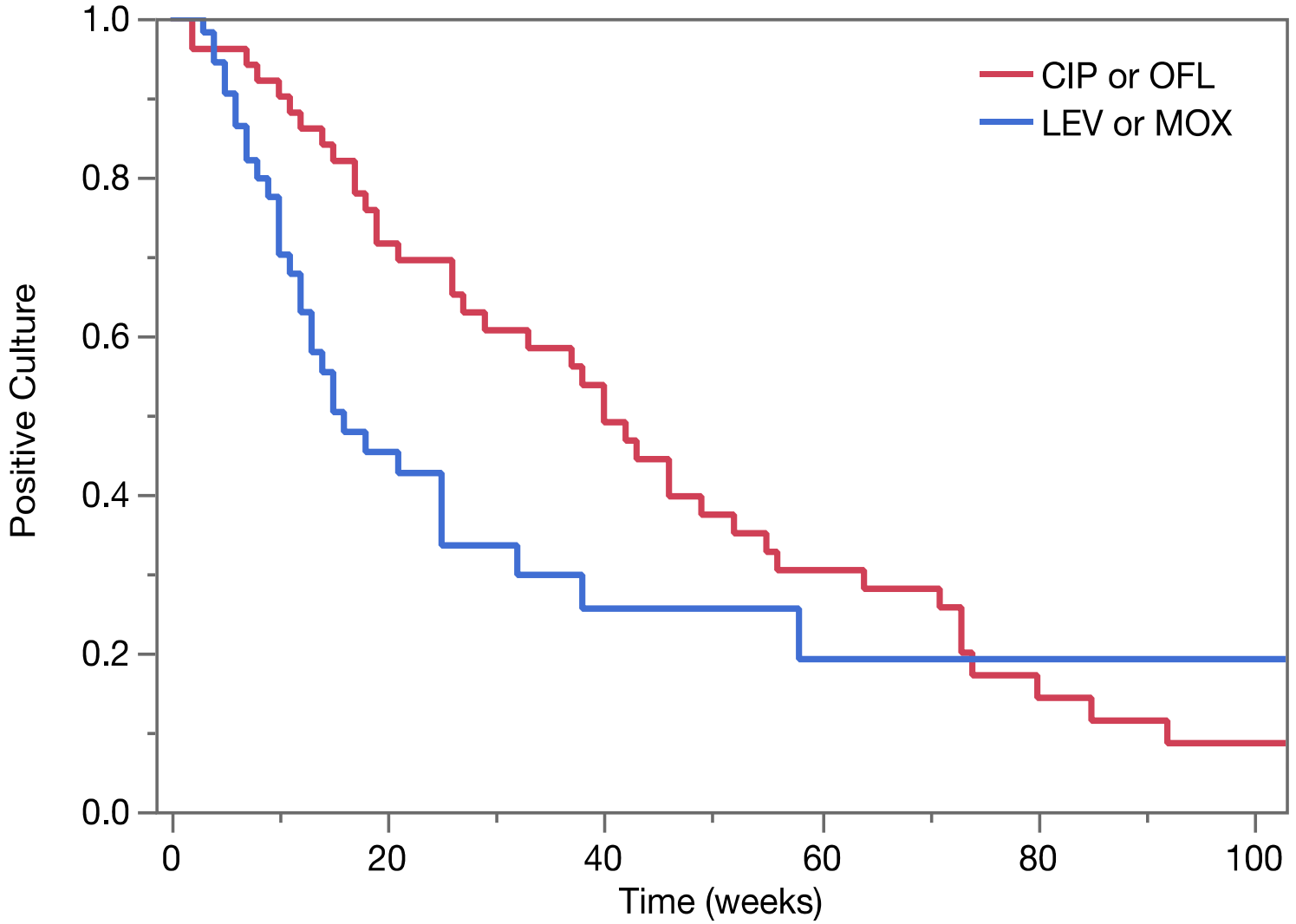
- 106 MDR-TB patients received FQs

Characteristics	Median (range) or % (n)
Age, years	40 (15-92)
Sex, male	74% (78)
Weight, kg	59 (38-105)
FQ received **LVX/MOX** **CIP/OFL**	 52% (55) 48% (51)
Cavitary disease	20% (21)

Results

- Median 16 (LVX/MOX) vs. 40 (CIP/OFL) weeks

- Log-Rank p=0.0577
- Wilcoxon p=0.0035



Number at risk						
CIP/OFL	51	34	23	13	6	3
LEV/MOX	55	18	6	3	1	1

Results

- 52 patients had treatment outcome

- LVX (n=16): 10 (63%) cured
- MOX (n=36): 23 (64%) cured

- Serum concentration, median (range)

    - LVX : 9.2 mg/L (1.2-19.0)
    - MOX: 3.8 mg/L (0.9-10.4)

Results

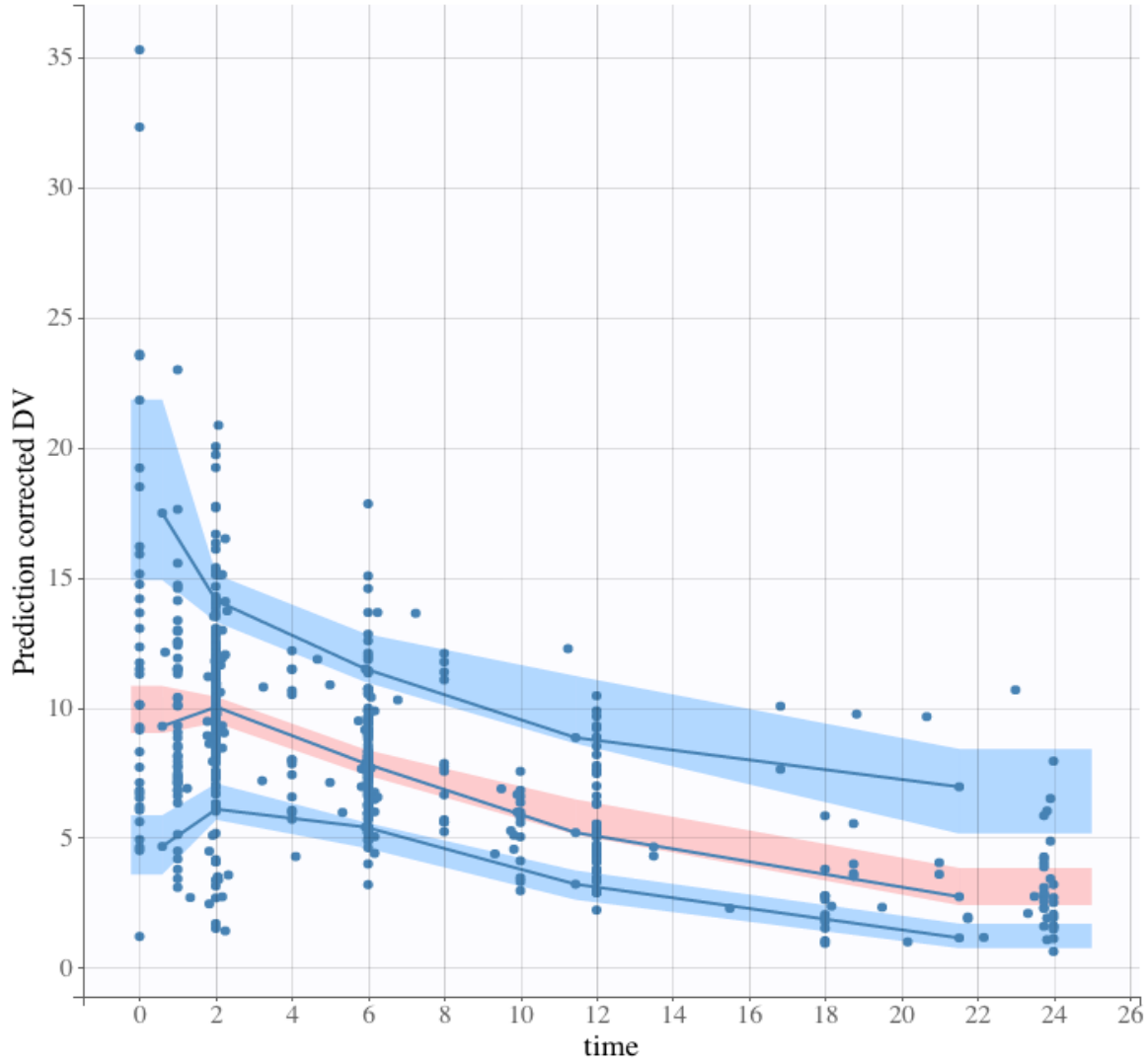
- Population PK models

- Additional data sources:

    - TBRU, Brazil
    - ISTC, Georgia
    - UVA Study, Bangladesh

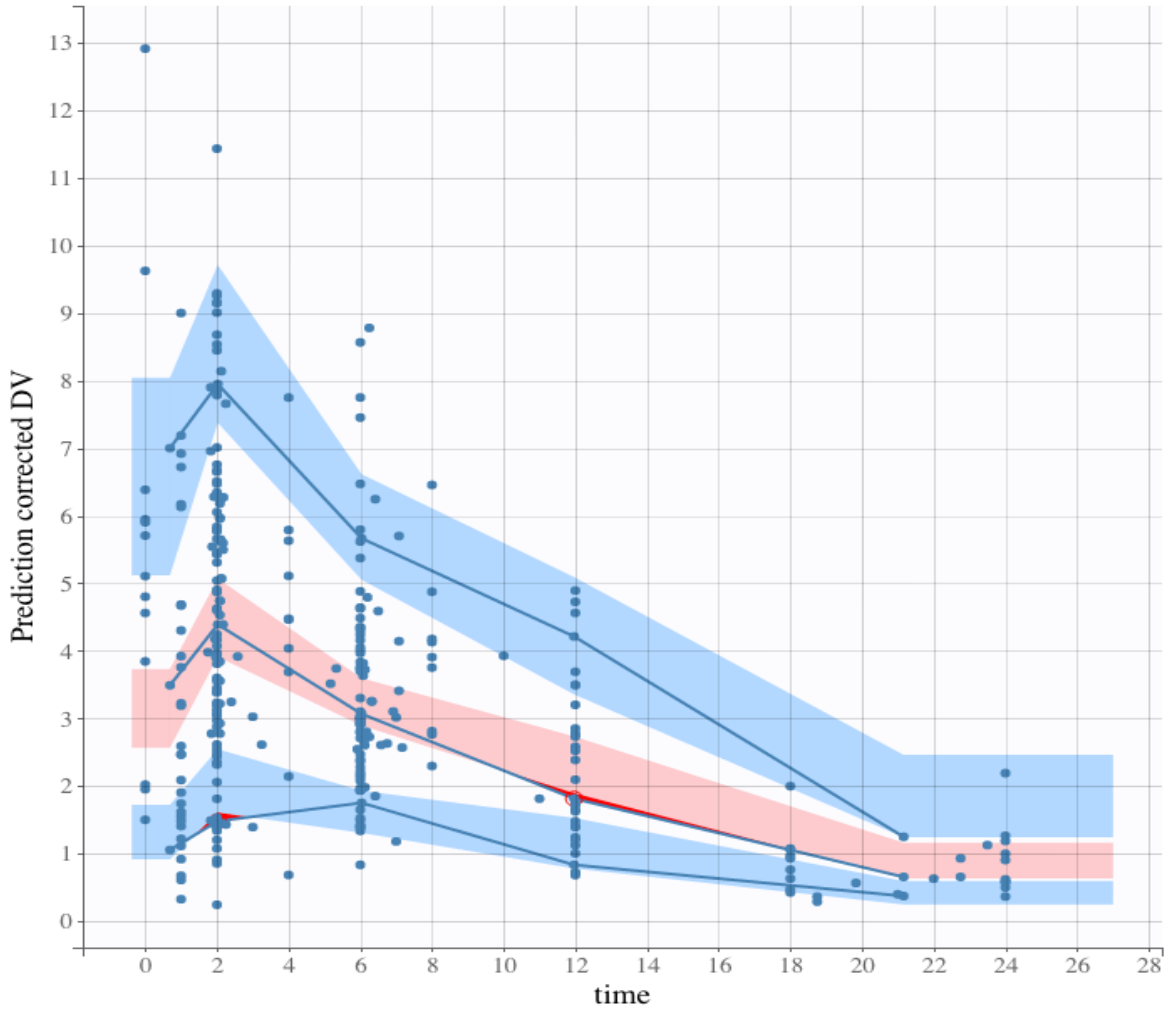
Results, Levofloxacin

FIXED EFFECTS			
Parameter	**Estimate**	**SE**	**RSE (%)**
ka (h^{-1})	3.82	2.43	63.6
V/F (L)	79.4	2.95	3.71
CL/F (L/h)	4.94	0.36	7.28
beta, CrCL on CL/F	0.52		
beta, Sex(M) on CL/F	0.28	0.08	29.5
RANDOM EFFECTS			
Omega, ka	1.55	0.47	30.2
Omega, V/F	0.18	0.04	23.6
Omega, CL/F	0.17	0.09	53.7
Gamma, CL/F	0.27	0.05	17.8
ERROR MODEL PARAMETERS			
Proportional	0.2	0.01	4.22



Results, Moxifloxacin

FIXED EFFECTS			
Parameter	**Estimate**	**SE**	**RSE (%)**
ka (h^{-1})	3.39	2.91	85.90
V/F (L)	124	36.30	29.30
CL/F (L/h)	9.32	0.74	7.92
RANDOM EFFECTS			
Omega, ka	2.1	0.47	22.30
Omega, V/F	0.40	0.29	71.40
Omega, Cl/F	0.31	0.06	20.10
ERROR MODEL PARAMETERS			
Proportional	0.35	0.02	5.45



Results

- EBEs and target attainment

	LVX (n=25) Median (range) or % (n)	MOX (n=26) Median (range) or % (n)
Cmax, mg/L	9.9 (6.4-16.1)	4.0 (2.9-8.3)
AUC_{0-24}, mg.hr/L	118.8 (76.7-287.6)	46.1 (28.7-90.9)
*f*Cmax/MIC >10	4% (1)	46% (12)
fAUC_{0-24}/MIC >100	32% (8)	73% (19)

- Treatment outcome available for 8 patients (6 LVX, 2 MOX) who had EBEs generated. Cured: 5 LVX, 0 MOX

Conclusion

- In MDR-TB patients, LVX and MOX showed faster time to culture conversion compared to CIP and OFL.

- Higher percentage of patients achieved the PK/PD target in MOX compared to LVX, which may indicate that higher doses of LVX are needed.

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