European Respiratory Society
Annual Congress 2012

Abstract Number: 4832

Publication Number: P2716

Abstract Group: 10.2. Tuberculosis

Keyword 1: Pharmacology **Keyword 2:** Tuberculosis - management **Keyword 3:** Infections

Title: Pharmacokinetics and drug susceptibility testing imply limited activity of current regimens for Mycobacterium avium complex disease

Dr. Jakko 30065 van Ingen jakko.vaningen@gmail.com MD , Dr. Martin 30066 Boeree m.boeree@uccz.umcn.nl MD , Prof. Charles 30067 Peloquin peloquin@cop.ufl.edu and Prof. Charles 30068 Daley daleyc@njhealth.org MD . [1] Medical Microbiology, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands ; [2] Pulmonary Diseases, Radboud University Nijmegen Medical Center, Nijmegen, Netherlands ; [3] Emerging Pathogens Institute, University of Florida, Gainesville, FL, United States and [4] Mycobacterial and Respiratory Infections, National Jewish Health, Denver, CO, United States .

Body: Background: Treatment outcome in Mycobacterium avium complex (MAC) lung disease is poor, with cure rates of 50-70%. To understand this, we retrospectively assessed the pharmacokinetics and MICs of key drugs in MAC disease treatment. Methods: Pharmacokinetic and drug susceptibility data of all patients admitted at National Jewish Health, Denver, USA, in the January 2006-June 2010 period was retrieved from databases. Pharmacokinetic measurements were done by high performance liquid chromatography and gas chromatography. Isolates were identified as MAC by AccuProbe assays. MICs were determined by the BacTec460 macrodilution method; synergy between rifampicin and ethambutol was assessed. Results: Pharmacokinetic data, median MICs and pharmacodynamic calculations are given in Table 1. Simultaneous use of rifampicin significantly lowered serum concentrations of macrolides (30-60%) and moxifloxacin (10-15%).

Average serum concentrations and pharmacokinetic calculations

Drug	Mean Cmax	Mean AUC	PD target	Median MIC	% above PD target
Rifampicin (n=299)	18.55±6.75	68.42±24.26	AUC/MIC >271; Free AUC/MIC >24.14	2	6%; 18%
Ethambutol (n=421)	2.24±1.02	10.18±4.35	Free Cmax/MIC >1.23	1	57%
Azithromycin (n=367)	0.32±0.23	1.47±1.00	n.a.	n.a.	n.a.
Clarithromycin (n=59)	2.26±1.87	10.67±9.53	T50%>MIC	≤4	n.a.
Moxifloxacin (n=96)	4.25±1.51	18.81±6.46	Cmax/MIC >10 ; AUC/MIC >100	2	11%; 0%

Conclusions: Serum rifampicin, ethambutol and moxifloxacin concentrations attain effective levels in a minority of patients; rifampicin use exerts detrimental effects on pharmacokinetics of macrolides and moxifloxacin. This may partly explain the poor outcomes of MAC disease treatment.