Lower Dose-Adjusted Concentrations of Rifampicin and Pyrazinamide in Pulmonary versus Extra-Pulmonary Tuberculosis

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Background: Rifampicin, isoniazid and pyrazinamide compose first-line treatment of drug-susceptible tuberculosis (TB). Dose-dependent efficacy has been demonstrated for rifampicin, and low pyrazinamide levels are associated with unfavorable outcomes. It is unknown whether subtherapeutic drug exposure is more prevalent in pulmonary (PTB) versus extrapulmonary TB (EPTB), which often presents with lower disease burden such as lymph node TB. Identification of clinical phenotypes associated with low drug concentrations can be important for individualized dose optimization and better treatment outcomes. The aim of this study is to compare plasma concentrations of the first-line drugs in PTB and EPTB.

Methods: We investigated first-line drug concentrations among adult patients with PTB and EPTB in two Swedish study cohorts. In the first prospective cohort (*n*=31), drug concentrations were measured pre-dose and at 2, 4, and 6 hours after dose intake at 2 weeks. The second retrospective cohort (*n*=72), provided results from routine therapeutic drug monitoring (TDM) with minimum blood sampling 2 hours after drug intake. PTB and EPTB classification followed WHO guidelines. Drug concentration analysis was performed using liquid chromatography mass spectrometry. Lower than recommended peak drug concentrations were defined as rifampicin <8 mg/L, isoniazid <3 mg/L, and pyrazinamide <35 mg/L. The concentration/dose (C/D) ratio was calculated by dividing the peak concentration (mg/L) with the dose (mg/kg). Mann-Whitney U test was used for statistical analyses and *p*-value <0.05 was considered statistically significant.

Results: Median (IQR) age was 33 years (23.5-42.5) and 50.5% were female. All 103 patients but three were HIV-negative and 68% (19/28) of EPTB patients were lymph node TB. Among PTB 15.6% (7/45) of the patients were sputum culture positive 2 months after treatment initiation, indicating slow treatment response. Relapse within 12 months after treatment completion was observed in three immunocompetent PTB patients out of 61 evaluable and in one immunocompromised EPTB patient out of 22 evaluable. Patients with PTB received significantly higher doses (mg/kg) of rifampicin (10.3 [8.5-12.1] and 9.0 [8.0-

10.0], *p*=0.002) and isoniazid (5.0 [4.4-5.6] and 4.3 [3.8-4.8], *p*=0.004) compared with EPTB, meanwhile, pyrazinamide doses were similar (24.9 [22.2-27.6] and 24.2 [22.0-26.5], *p*=0.32). The proportion of PTB with lower than recommended drug levels of rifampicin, isoniazid and pyrazinamide was 36%, 31% and 35% and for EPTB 20%, 36% and 20%, respectively. C/D-ratio was significantly lower for PTB compared with EPTB for rifampicin (median 0.90 [IQR 0.6-1.2] versus 1.40 [1.0-1.8], *p*=0.004) and pyrazinamide (1.50 [1.3-1.7] versus 1.67 [1.3-2.0], *p*=0.016). C/D-ratio for isoniazid did not differ between PTB and EPTB (0.76 [0.51-1.02] versus 0.87 [0.56-1.19], *p*=0.33), but fast acetylators exhibited significantly lower median (IQR) isoniazid C/D-ratio compared with slow acetylators (0.60 [0.38-0.82] and1.20 [0.88-1.52], P<0.001).

Conclusion: Despite higher or similar doses, subtherapeutic drug levels of rifampicin and pyrazinamide were nearly twice as common in patients with PTB compared with EPTB with significantly lower C/D-ratios of both drugs in PTB, which indicates that the clinical phenotype may affect drug exposure and highlights the importance of TDM-guided dose optimization of these sterilizing drugs.