Pharmacogenetics and pharmacokinetics of moxifloxacin in MDR-TB patients in Indonesia: analysis for *ABCB1* rs2032582 and *SLCO1B1* rs4140915

Nurul Annisa[1,2], Nadiya N. Afifah[1,3], Prayudi Santoso[4,5], Vycke Yunivita[5,6], Lindsey H. M. te Brake[7], Rob E. Aarnoutse[7], Melisa I. Barliana[1,8*], and Rovina Ruslami[5,6]

Affiliations:

[1]Department of Biological Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia

[2]Division of Clinical and Community Pharmacy, Faculty of Pharmacy, Universitas Mulawarman, Samarinda, Indonesia

[3]Department of Pharmacy, Faculty of Health Sciences, Universitas Esa Unggul, Jakarta, Indonesia

[4]Division of Pulmonary and Critical Care, Faculty of Medicine, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran/Hasan Sadikin General Hospital, Bandung, Indonesia

[5]Research Center for Care and Control of Infectious Disease, Universitas Padjadjaran, Bandung, Indonesia

[6]Division of Pharmacology and Therapy, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

[7]Department of Pharmacy, Radboud Institute for Medical Innovation, Radboud university medical center, Nijmegen, The Netherlands

[8]Center of Excellence for Pharmaceutical Care Innovation, Universitas Padjadjaran, Sumedang, Indonesia

ABSTRACT

Introduction

Moxifloxacin is categorized as a group A drug for multi-drug resistant TB (MDR-TB) and is used in 9-11 months of MDR-TB treatment regimens. Polymorphism in the genes *ABCB1* and *SLCO1B1* may affect the pharmacokinetics (PK) of moxifloxacin. This study aimed to (1) assess the genotype frequencies of *ABCB1* rs2032582 and *SLCO1B1* rs4140915, (2) describe the $AUC_{0\text{-}24}$ and C_{max} of moxifloxacin, and (3) evaluate the association between polymorphisms and moxifloxacin $AUC_{0\text{-}24}$ and C_{max}, corrected for the effect of other predictors in Indonesian MDR-TB patients.

Methods

Adult (>18 years old) MDR-TB patients who received a short-course (9-11 months) regimen containing moxifloxacin (400 or 600 mg once daily) were recruited for the study. Genotyping was done by sequencing. Plasma samples for PK analysis were collected at either four or two-time points (at 0, 2, 4, and 6 hours or 0, 2 hours post-dose) at a steady state. Moxifloxacin concentrations were measured by HPLC-UV. $AUC_{0\text{-}24}$ was estimated using limited sampling equations by Magis et al (2014). C_{max} values were directly derived from the measured concentrations. Multiple linear regression identified predictors of moxifloxacin $AUC_{0–24}$ and C_{max}.

Results

A total of 204 MDR-TB patients were recruited for pharmacogenetic analysis, with 80 providing PK samples. The median dose of moxifloxacin was 10.3 mg/kg. Most of the genotypes identified of *ABCB1 rs2032582* were wildtype (GG, 41.7%) and GT (37.7%), whereas for *SLCO1B1rs4149015 the GG* genotype represented 93.6%. The geometric mean $AUC_{0\text{-}24}$ for moxifloxacin was 79 mg·h/l and 6.2 mg/l for C_{max}. Multiple linear regression analysis revealed that gender, age, and dose in mg/kg predicted the $AUC_{0\text{-}24}$ of moxifloxacin, whereas gender and dose in mg/kg affected C_{max}. Patients with the TT genotype of *ABCB1* showed moxifloxacin $AUC_{0–24}$ and C_{max} values lower than the average (53.3 mg.h/l and 4.3 mg/l, respectively). Conversely, individuals with the GA genotype of *SLCO1B1* exhibited moxifloxacin $AUC_{0–24}$ and C_{max} values higher than average (128.2 mg.h/l and 8.3 mg/l,

respectively), but none of these relationships between pharmacogenetics and pharmacokinetics reached statistical significance.

Conclusions

Exposure to moxifloxacin in Indonesian MDR-TB patients is high, circa two-fold higher than in other populations, due to a combination of low weight and use of a high dose (600 mg) in part of the population. Gender, age, and dose/body weight are predictors for AUC_{0-24} and C_{max} of moxifloxacin. Future studies exploring the interplay between PG and PK in larger populations are warranted.