Title: Population pharmacokinetic modeling of rifampicin at standard and high doses in adults with tuberculous meningitis

Noha Abdelgawad (1), Sean Wasserman (2,3), Kamunkhwala Gausi (1), Angharad Davis (2,5,6), Cari Stek (2) Lubbe Wiesner (1), Robert J. Wilkinson (2,4,5,7), Paolo Denti (1)

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Observatory 7925, South Africa

(2) Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Observatory 7925, South Africa

(3) Institute for Infection and Immunity, St George's University of London, United Kingdom

(4) Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Observatory 7925, South Africa

(5) The Francis Crick Institute, London NW1 1AT, United Kingdom

(6) Faculty of Life Sciences, University College London, WC1E 6BT, United Kingdom

(7) Department of infectious Diseases, Imperial College London W12 0NN, United Kingdom

Background:

Tuberculous meningitis (TBM) is the deadliest form of tuberculosis (TB) and people with HIV are at especially high risk [1]. The standard TBM treatment regimen is based on that of pulmonary TB, which does not consider the ability of drugs to cross the blood-brain barrier, possibly leading to suboptimal exposures at the site of disease. Saturable elimination has been reported for higher rifampicin doses [2]. After repeated dosing, rifampicin induces its own clearance via inducing its metabolizing enzymes, with clearance predicted to double after 2 weeks [3]. A number of clinical trials have demonstrated improved efficacy of higher rifampicin doses in TB [4,5]. High-dose rifampicin is currently being evaluated in several clinical trials for TBM. Pharmacokinetics (PK) of high-dose rifampicin is not well characterized in TBM/HIV patients. The objective of this study was to describe the plasma and CSF population PK of standard- (10mg/kg) versus high-dose (35mg/kg) daily rifampicin in adults with TBM/HIV.

Methods:

This PK study was nested within the Phase 2 LASER-TBM trial, which enrolled adults with TBM/HIV in South Africa within 5 days of starting standard TB treatment. The participants were randomized into one of three groups: a control arm that received standard TB regimen and two experimental arms that received additional

rifampicin (total dose 35mg/kg) plus linezolid, with or without aspirin. Participants in both experimental arms underwent a second randomization to receive rifampicin orally (35mg/kg) or intravenously (IV) (20mg/kg) for the first 3 days. Plasma samples were collected at pre-dose, and at 0.5, 1, 2, 3, 6, 8-10, and 24 hours post-dose on day 3 of enrolment and at pre-dose, 2, and 4 hours post-dose on day 28. One lumbar CSF sample was withdrawn on each PK visit. Concentrations were determined using LC-MS/MS. Different structural models were tested, including 1- and 2-compartment, with linear elimination or saturable hepatic extraction. Allometric scaling of all disposition parameters was tested by either weight or fat-free mass (FFM). The CSF concentrations were described using a hypothetical effect compartment linked to the central (plasma) compartment, which estimates a CSF-plasma ratio and an equilibration half-life.

Results:

415 rifampicin plasma concentrations from 49 participants were included in this analysis. The participants median (min-max) age, weight, and fat-free mass (FFM) were 38 (25-56) years, 60 (30-96)kg, and 46 (23-60)kg, respectively. Rifampicin PK was best described by a 2-compartment disposition, first-order absorption with lag time and elimination with saturable hepatic extraction. The prehepatic oral bioavailability was estimated to be 97%. The typical values of CL_{int} on day 3 were 234 L/h for high-dose and 169 L/h for standard-dose, and on day 28, they were 359 L/h for the high-dose and 233 L/h for the standard-dose. The estimates for the Michaelis-Menten constant, central volume of distribution, intercompartmental clearance, and peripheral volume of distribution were 2.75 mg/L, 24.9 L, 12.6 L/h, and 36.7 L. All disposition parameters were allometrically scaled by FFM. The CSF-plasma ratio was estimated to be 7% and the equilibration half-life was 3.5 hours.

Conclusion:

A population PK model was developed describing PK of rifampicin in adult TBM/HIV patients, which is in line with previous reports [3,6,7]. By including observations from both IV and oral administration, we were able to define a 2-compartment disposition. Additional research is required to ascertain whether high-dose rifampicin would result in higher exposures at site of disease. This model provides a platform for such further investigations.

References:

1. Thwaites GE, Bang ND, Dung NH, Quy HT, Oanh DTT, Thoa NTC, et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with Tuberculous meningitis. J Infect Dis [Internet]. J Infect Dis; 2005 [cited 2022 Apr 4];192:2134–41. Available from: https://pubmed.ncbi.nlm.nih.gov/16288379/

2. Acocella G. Pharmacokinetics and Metabolism of Rifampin in Humans. Clin Infect Dis [Internet]. 1983;5:S428–32. Available from: http://academic.oup.com/cid/article/5/Supplement_3/S428/275576/Pharmacokinetics-and-Metabolism-of-Rifampin-in

3. Chirehwa MT, Rustomjee R, Mthiyane T, Onyebujoh P, Smith P, McIlleron H, et al. Model-Based Evaluation of Higher Doses of Rifampin Using a Semimechanistic Model Incorporating Autoinduction and Saturation of Hepatic Extraction.[Erratum appears in Antimicrob Agents Chemother. 2016 May;60(5):3262; PMID: 27107106]. Antimicrob Agents Chemother. 2015;60:487–94.

4. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis [Internet]. Lancet Publishing Group; 2017 [cited 2022 Oct 15];17:39–49. Available from: http://www.thelancet.com/article/S1473309916302742/fulltext

5. Boeree MJ, Diacon AH, Dawson R, Narunsky K, Du Bois J, Venter A, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med [Internet]. American Thoracic Society; 2015 [cited 2022 Oct 16];191:1058–65. Available from: www.clinicaltrials.gov

6. Savic R, Ruslami R, Hibma J, Hesseling A, Ramachandran G, Ganiem A, et al. Pediatric tuberculous meningitis: Model-based approach to determining optimal doses of the anti-tuberculosis drugs rifampin and levofloxacin for children. Clin Pharmacol Ther [Internet]. 2015;98:622–9. Available from: https://onlinelibrary.wiley.com/doi/10.1002/cpt.202

7. Svensson EM, DIan S, Te Brake L, Ganiem AR, Yunivita V, Van Laarhoven A, et al. Model-Based Meta-analysis of Rifampicin Exposure and Mortality in Indonesian Tuberculous Meningitis Trials. Clin Infect Dis. 2020;71:1817–23.