Title: Model-informed once-daily dosing strategy for bedaquiline and delamanid in children, adolescents and adults with tuberculosis

Authors: Yu-Jou Lin (1), Louvina E. van der Laan (2), Mats O. Karlsson (1), Anthony J. Garcia-Prats (2,3), Anneke C. Hesseling (2), Elin M. Svensson (1,4)

Institution:
(1) Department of Pharmacy, Uppsala University, Uppsala, Sweden,
(2) Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa,
(3) Department of Pediatrics, University of Wisconsin-Madison, Madison, Wisconsin, USA,
(4) Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands

Introduction:
The complexity of the currently registered dosing schedules for bedaquiline [1] and delamanid [2] is a barrier to uptake in drug-resistant tuberculosis treatment in people across all ages. Simpler once-daily dosing schedule is critical to ensure patient-friendly regimens with good adherence. We applied modeling and simulation approaches to assess expected drug exposures with proposed once-daily doses for adults, and compare novel model-informed once-daily dosing strategies for children with current World Health Organization (WHO) recommended dosing [3].

Methods:
To simulate typical adult exposures, a reference individual (32-year-old, non-black race, 56.6 kg and 3.65 g/dL of baseline albumin level) was used. 40,000 pediatric patients were simulated with age uniformly distributed from 0 to <15 years, 50%/50% gender split and 40% of black race. The weight-per-age distribution was based on WHO growth curves and data from the National Health and Nutrition Examination Survey [4,5], adjusted by a factor for TB disease [6].

Published population models characterizing the exposure of bedaquiline and its metabolite M2 [7] and delamanid and its metabolite DM-6705 [8] in adults were utilized. For simulation of bedaquiline and M2 exposures in children, the Svensson adult model [7] served as a base and was adapted to the pediatric population with the following adjustments: 1) the scaling value of 0.75 was used for clearances and 2) the effect of albumin levels on clearances was not included. For delamanid and DM-6705, the Sasaki pediatric model [9] was utilized. Given the limited information on bioavailability in children < 1 year of age, two scenarios (constant or linearly decreased bioavailability with age below 1 year) were tested. During simulation, child growth along with three CYP3A4 ontogeny profiles (Johnson, Salem and Upreti) [10–12] were

accounted for. Exposures in children were compared with simulated adult targets to assess the expected treatment efficacy and safety.

Results:
In adults, proposed bedaquiline once-daily dosing yielded 14% higher exposures of bedaquiline and M2 compared to the labelled dosing scheme at 24 weeks; for delamanid and DM-6705, the suggested 300-mg daily dose provided 13% lower exposures at steady-state. For children, the cumulative proportions of exposures of both drugs and their metabolites showed less than 5% difference between WHO-recommended and proposed once-daily dosing regimens. Systematically higher exposures of bedaquiline (9.1-15%) and M2 (23-40%) and lower exposures of delamanid (14-25%) and DM-6705 (5.6-25%) with proposed once-daily doses were observed compared to the WHO-recommended doses. Simulation results indicated that more than 90% of children aged < 1 year were within the target range of bedaquiline and M2 while using Johnson and Salem ontogenies, whereas 34% of them were below the target range using Upreti ontogeny. Despite high simulated exposures of DM-6705 with Salem ontogeny under proposed once-daily doses, the exposures were within the adult target range.

Conclusion:
This study demonstrated the use of model-informed approaches to propose rational and simpler dosing regimens for bedaquiline and delamanid in adults and children. The new once-daily dosing strategies will be tested in the UNITE4TB PARADIGM4TB and IMPAACT 2020 trials in adults and children, respectively.

Funding

The project was funded from the National Institute of Health through the International Maternal Pediatric Adolescent AIDS Clinical Trials Network under award number UM1AI068632-17 for IMPAACT 2020 and the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101007873 for UNITE4TB. Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA, Deutsches Zentrum für Infektionsforschung e. V. (DZIF), and Ludwig-Maximilians-Universität München (LMU). EFPIA/AP contribute to 50% of funding, whereas the contribution of DZIF and the LMU University Hospital Munich has been granted by the German Federal Ministry of Education and Research. AC. Hesseling is also supported by a South African National Research Foundation SARchi Chair.

References

1. U.S. Food and Drug Administration. Sirturo (bedaquiline) label [Internet]. 2012 [cited 2024 Jan 5]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf
2. European Medicines Agency. Deltyba: European public assessment report (EPAR) - Product Information [Internet]. 2013 [cited 2024 Jan 5]. Available from: https://www.ema.europa.eu/en/documents/product-information/deltyba-epar-product-information_en.pdf
3. World Health Organization. WHO operational handbook on tuberculosis 2022 module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization; 2022.
4. World Health Organization. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development [Internet]. 2006 [cited 2024 Jan 22]. Available from: https://www.who.int/publications/i/item/924154693X
5. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002;(246):1–190.

6. Svensson EM, Yngman G, Denti P, McIlleron H, Kjellsson MC, Karlsson MO. Evidence-Based Design of Fixed-Dose Combinations: Principles and Application to Pediatric Anti-Tuberculosis Therapy. Clin Pharmacokinet. 2018;57(5):591–9.
7. Svensson EM, Dosne A, Karlsson MO. Population Pharmacokinetics of Bedaquiline and Metabolite M2 in Patients With Drug-Resistant Tuberculosis: The Effect of Time-Varying Weight and Albumin. CPT Pharmacomet Syst Pharmacol. 2016 Dec;5(12):682–91.
8. Tanneau L, Karlsson MO, Diacon AH, Shenje J, De Los Rios J, Wiesner L, et al. Population Pharmacokinetics of Delamanid and its Main Metabolite DM-6705 in Drug-Resistant Tuberculosis Patients Receiving Delamanid Alone or Coadministered with Bedaquiline. Clin Pharmacokinet. 2022 Aug;61(8):1177–85.
9. Sasaki T, Svensson EM, Wang X, Wang Y, Hafkin J, Karlsson MO, et al. Population Pharmacokinetic and Concentration-QTc Analysis of Delamanid in Pediatric Participants with Multidrug-Resistant Tuberculosis. Antimicrob Agents Chemother. 2022 Feb 15;66(2):e01608-21.
10. Johnson TN, Rostami-Hodjegan A, Tucker GT. Prediction of the Clearance of Eleven Drugs and Associated Variability in Neonates, Infants and Children: Clin Pharmacokinet. 2006;45(9):931–56.
11. Salem F, Johnson TN, Abduljalil K, Tucker GT, Rostami-Hodjegan A. A Re-evaluation and Validation of Ontogeny Functions for Cytochrome P450 1A2 and 3A4 Based on In Vivo Data. Clin Pharmacokinet. 2014 Jul;53(7):625–36.
12. Upreti VV, Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J Clin Pharmacol. 2016 Mar;56(3):266–83.