Population pharmacokinetics of sutezolid and its main metabolite to characterize the exposure-response relationship in patients with pulmonary tuberculosis

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Abstract

Background: The current WHO guidelines for the treatment of multi-drug-resistant tuberculosis (MDR-TB) recommend that linezolid, an oxazolidinone, is a preferred drug in the MDR-TB treatment regimen (1). However, linezolid therapy is associated with high adverse effect rates, resulting in treatment interruptions or dose reductions in 27% of all patients (2). Sutezolid, a novel oxazolidinone, is a candidate to replace linezolid in the treatment of MDR-TB. Previous studies have indicated sutezolid to be equally active, and potentially less toxic compared with linezolid (3, 4). Sutezolid is metabolized into an active metabolite, which may contribute to its overall efficacy (4). Characterization of the exposure-response relationship for sutezolid could aid in dose selection and clinical trial design.

Objective: We aimed to develop a parent-metabolite pharmacokinetic-pharmacodynamic (PK-PD) model to characterize the exposure-response relationship for sutezolid.

Methods: A phase 2b, open-label, multicentre, randomized controlled, clinical trial (SUDOCU) was performed, and the main results were previously presented (5). In total, 75 patients with drug-susceptible pulmonary TB were enrolled in Tanzania and South Africa. Participants were randomized to one of five treatment arms with different doses of sutezolid for 12 weeks. All arms were treated with a regimen consisting of bedaquiline, delamanid, and moxifloxacin in approved doses, and sutezolid was added as 0mg, 600mg QD, 1200mg QD, 600mg BD, or 800mg BD. Intensive plasma sampling was performed on day 14 at times 0,1,2,4,8,12, and 24 hours after the dose. Trough plasma samples were collected on days 7,14,28,56, and 84. Sutezolid and metabolite concentrations were determined using validated LC-MS/MS assays.

Sputum samples were collected weekly for 12 weeks and the time-to-positivity (TTP) in liquid culture, representing the bacterial load, was determined. Linear and bi-linear models were evaluated to describe the decrease in bacterial load over time. The M3 method, incorporating a partial likelihood, was used to account for observations that were above a censoring limit (25 days) (6). The exposure-response relationship for sutezolid was evaluated based on individual exposure metrics during steady-state.

Results: In total, 373 plasma concentrations were available for both sutezolid and its metabolite. The PK was best described by a 2-compartment disposition model for sutezolid and a 2-compartment model for the metabolite. A well-stirred liver model was used to describe the metabolism of sutezolid. The absorption was best described using dynamically estimated transit compartments. Inter-occasion variability was identified on the bioavailability, and interindividual variability on all clearance parameters, mean transit time, and the absorption rate constant. Allometric scaling was used on all disposition parameters based on total body weight. Stepwise covariate modeling did not identify any other relevant covariates. Median AUC_{0-24} (mg/L*h) based on individual predictions were 3.52 for 600mg QD, 6.79 for 1200mg QD, 8.29 for 600mg QD, and 11.18 for 800mg BD treatment arms. Metabolite AUC_{0-24} was on average a factor 5-fold higher than sutezolid AUC_{0-24}.

For the PD model, 1651 culture results were available. A bi-linear model with an estimated node parameter at around 8 weeks obtained the best fit describing the increase in TTP over

time. Baseline bacterial load was identified as being associated with the steepness of the first slope and the extent of lung damage was associated with the second slope. The exposure-response relationship for sutezolid was best described by a linear effect of sutezolid AUC_{0-24} on both slope parameters (p=0.04). Participants in the upper quantile of observed sutezolid AUC_{0-24} were predicted to typically have 17% (95% CI 1%-37%) steeper slopes compared to participants not receiving sutezolid. No exposure-response relationship for the metabolite was detected.

Conclusion: In summary, a modest relationship between sutezolid exposure and decrease in bacterial load was identified. The maximal effect was not observed within the investigated dose range, and therefore, it was not possible to predict a maximum effective dose. Sutezolid AUC_{0-24} was identified as the driver of the antimicrobial effect. Furthermore, the population PK-PD model we developed provides a valuable tool for further clinical trial design and dose optimization.

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