Delpazolid population pharmacokinetics and pharmacodynamics in patients with pulmonary tuberculosis

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DElpazolid dose-finding and COmbination DEvelopment (DECODE)

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Abstract

Introduction Linezolid is currently recommended for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the WHO. However, this drug is associated with severe adverse effects such as myelosuppression and peripheral neuropathy [1]. Delpazolid, a new oxazolidinone, has demonstrated early bactericidal activity with a favorable safety profile when administered up to 14 days [2]. Therefore, if shown effective and with a lower risk of adverse effects over longer treatment durations [3], delpazolid could be a promising alternative for linezolid in MDR-TB treatment.

Methods The DECODE study was a phase 2b trial performed in South Africa and Tanzania. 76 adult patients with drug-sensitive pulmonary TB were included and delpazolid was administered in combination with standard-dose bedaquiline, delamanid and moxifloxacin over 16 weeks. Patients were randomized into one of the five arms receiving 0 mg, 400 mg, 800 mg, or 1200 mg QD, or 800 mg BID. Intensive PK sampling was conducted in all patients on day 14 of treatment, with samples taken at 0 (pre-dose) and 1, 2, 4, 8, 10, 12, and 24 hours after dosing. Drug concentrations in plasma were determined using a validated LC-MS/MS combination assay covering all analytes. Sputum samples were collected every week during the treatment period. Delpazolid efficacy was evaluated by measuring the change in mycobacterial load in sputum over time. It was quantified by time to positivity (TTP), the time from start of incubation to detection of mycobacteria by their metabolic activity in mycobacterial growth incubator tubes (MGIT)[4, 5]. A population PK-PD model was developed using non-linear mixed effects methodology implemented in NONMEM. The censoring limit used for TTP was 25 days[6].

Results The population PK model was developed based on 402 plasma concentrations from 60 patients (14 women and 46 men). A two-compartment model with first-order absorption, first-order elimination and a proportional residual error described delpazolid PK well. The final model included allometric scaling based on fat-free mass (FFM).[7] Delpazolid clearance was 38.1 L/h (95% CI 34.5-41.7) for a FFM of 58kg. Based on individual predictions, median $AUC_{0\text{-}24}$ (mg/L*h) values were 10.1 for 400 mg, 28.6 for 800 mg, 47.0 for 1200 mg (all QD), and 68.5 for 800mg BID. 2312 TTP results from 75 participants (1 person withdrawn before PK sampling was excluded) were used. A bi-linear model with upper limit of quantification at 25 days described log-transformed TTP data well. A linear effect of delpazolid $AUC_{0\text{-}24}$ up 50 mg/L*h on the second slope could be detected (p=0.025). The estimated maximal effect was 38% steeper second slope, but the 95% confidence interval was wide (4.2 – 83%). The observed median $AUC_{0\text{-}24}$ of the 1200 mg delpazolid dose (47.0 mg/L*h) was close to the exposure estimated to generate maximal effect.

Conclusion and discussion Delpazolid exposures increased linearly with dose. The results from the PK-PD modelling indicate that delpazolid adds efficacy on top of the strong backbone regime consisting of bedaquiline, delamanid and moxifloxacin. From an efficacy standpoint, a dose of 1200 mg would be reasonable to move forward in development.

Primary Sources

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