Translational predictions of phase 2a first-in-patient efficacy studies for antituberculosis drugs

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Shareable abstract (@ERSpublications)
A translational pharmacology platform to predict early bactericidal activity https://bit.ly/3NoO89J

Cite this article as: Ernest JP, Goh JJN, Strydom N, *et al*. Translational predictions of phase 2a first-in-patient efficacy studies for antituberculosis drugs. *Eur Respir J* 2023; 62: 2300165 [DOI: 10.1183/13993003.00165-2023].

This article has an editorial commentary: https://doi.org/10.1183/13993003.01108-2023

Received: 25 Jan 2023
Accepted: 2 June 2023

Abstract

Background: Phase 2a trials in tuberculosis typically use early bactericidal activity (EBA), the decline in sputum CFU over 14 days, as the primary end-point for testing the efficacy of drugs as monotherapy. However, the cost of phase 2a trials can range from USD 7 million to USD 19.6 million on average, while >30% of drugs fail to progress to phase 3. Better utilising pre-clinical data to predict and prioritise the most likely drugs to succeed will thus help to accelerate drug development and reduce costs. We aim to predict clinical EBA using pre-clinical *in vivo* pharmacokinetic (PK)-pharmacodynamic (PD) data and a model-based translational pharmacology approach.

Methods and findings: First, mouse PK, PD and clinical PK models were compiled. Second, mouse PK-PD models were built to derive an exposure–response relationship. Third, translational prediction of clinical EBA studies was performed using mouse PK-PD relationships and informed by clinical PK models and species-specific protein binding. Presence or absence of clinical efficacy was accurately predicted from the mouse model. Predicted daily decreases of CFU in the first 2 days of treatment and between day 2 and day 14 were consistent with clinical observations.

Conclusion: This platform provides an innovative solution to inform or even replace phase 2a EBA trials, to bridge the gap between mouse efficacy studies and phase 2b and phase 3 trials, and to substantially accelerate drug development.