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Successful Translational Prediction of Bedaquiline's Phase 2a Clinical Trial Results against Tuberculosis: The Zebrafish as a New Approach Methodology

Abstract

Tuberculosis remains an urgent global health crisis that requires an accelerated development of novel regimens. Rodent and rabbit studies currently inform early translational predictions. However, the zebrafish (Danio rerio) embryo/larva, as a New Approach Methodology, provides an ethical, cost-effective, and high-throughput non-mammalian disease model to study early anti-tuberculosis drug pharmacology and bridge the gap between in vitro drug screens and (confirmatory) rodent experiments. This study aimed to translate the bedaquiline exposure–response relationship from zebrafish to humans to predict two phase 2a trial results in order to strengthen the use of zebrafish as a New Approach Methodology for translational anti-tuberculosis pharmacology. An established exposure–response relationship for bedaquiline in zebrafish against Mycobacterium marinum as a tuberculosis disease model was combined with a clinical population pharmacokinetic model to predict bacterial burden profiles from two published phase 2a clinical trials (25 to 400 mg daily). This translation incorporated the minimum inhibitory concentration ratio between Mycobacterium marinum and Mycobacterium tuberculosis to scale the zebrafish bedaquiline EC50 to humans. Clinical simulations based on the scaled zebrafish exposure–response relationship demonstrated that accounting for in vitro drug sensitivity resulted in close alignment with observed bacterial burden across all doses and timepoints, with a mean absolute percentage error of 10.37% and a root mean squared error of 0.74 log10 colony-forming units per milliliter of sputum. These findings demonstrate that early-phase clinical results for bedaquiline in tuberculosis can be successfully predicted from pharmacokinetics–pharmacodynamics in the zebrafish tuberculosis disease model. These results help advance the zebrafish as a resource-efficient and sustainable New Approach Methodology for tuberculosis drug development.

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