Power to identify exposure-response relationships in phase IIa tuberculosis trials with multi-dimensional bacterial load modeling.

Simon E. Koele[1], Thomas P.C. Dorlo[2], Caryn M. Upton[3], Rob Aarnoutse[1], Elin M. Svensson[1,2]

[1] Department of Pharmacy, Radboudumc Research Institute for Medical Innovation (RIMI), Radboud university medical center, Nijmegen, the Netherlands.

[2] Department of Pharmacy, Uppsala University, Uppsala, Sweden.

[3] TASK Applied Science, Cape Town, South Africa.

Abstract

Background: Demonstrating early bactericidal activity (EBA) in a phase IIa trial is one of the milestones in anti-TB drug development. The EBA of a drug is defined as the decrease in bacterial load in serial sputum measurements over 14 days and is thought to be driven by the exposure to a drug. The bacterial load is determined by the quantification of the colony-forming units (CFU) on solid culture and/or time-to-positivity (TTP) in liquid culture. The study of the EBA of a drug is also essential to inform the selection of the dose that will be carried forward into later-stage clinical trials. Therefore, adequate power to identify the exposure-response relationship of a drug in an EBA study is desirable. Currently, it is not known what method of bacterial load determination provides more power to identify an exposure-response relationship using a pharmacokinetic-pharmacodynamic (PK-PD) model.

Methods: We simulated CFU and TTP measurements for 14 days to determine the power of identifying an exposure-response relationship for four hypothetical drugs with similar pharmacokinetics but different exposure-response relationships.

The simulation model was based on CFU and TTP data gathered in the HIGHRIF1 trial (clinicaltrials.gov NCT01392911) (1, 2). In total, 796 CFU measurements and 800 TTP measurements were collected. Non-linear mixed-effects modeling was used to evaluate the most suitable pharmacodynamic model to describe the decrease in bacterial load. Linear, bi-linear, smooth bi-linear, and semi-mechanistic time-to-event models were evaluated (3, 4).

To simulate phase IIa clinical trial EBA data, each of the four hypothetical drugs was dosed daily in four groups receiving a low to high dosage, and sampling of CFU and TTP was simulated on days 0,1,2,3,4,5,7,10, and 14. The power to identify exposure-response relationships when analyzing CFU, TTP, or combined CFU+TTP data was determined for 60 participants (15 per dosing group) using Monte-Carlo mapped power analysis, or with 25 out of 60 participants in the lowest and highest dosing groups (unbalanced design) (5).

Results: The bi-linear model with estimated node-point was found to be the best model to describe both the CFU and TTP data from HIGHRIF1. Regardless of the EBA method used, drugs with a moderate bactericidal activity or late onset of activity showed power lower than 50% and 60%, respectively. Power was 1.9% to 29.4% higher when analyzing TTP data compared to CFU data. Combined analysis of CFU and TTP further improved the power, on average by 4.2%. For a drug with a medium-high activity, the total sample size needed to achieve 80% power was 136 for CFU, 72 for TTP, and 68 for combined CFU+TTP data. The unbalanced design improved the power by 16% over the balanced design.

Discussion: Power to identify an exposure-response relationship is low for TB drugs with moderate bactericidal activity or with a slow onset of activity for a typical study size. TTP provides more power

compared to CFU, and combined analysis or an unbalanced study design offers modest further improvement.

References

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