Added value of concentration-response over dose-response in estimating the ED_{50}

Alienor Berges, Monica Simeoni, Bart Laurijssens, Chao Chen
GlaxoSmithkline, Clinical Pharmacology Modelling & Simulation, Greenford, UK

Background & Objective

Identifying the dose with an optimal benefit-risk ratio is crucial in drug development, therefore confident and efficient characterisation of efficacy and toxicity as a function of dose is important. Using concentration-response relationship as a potentially more powerful tool for dose finding is increasingly appreciated. However, PK sampling is inconvenient; drug assays are costly and PKPD analysis may be time consuming. In this study, we attempted to quantify the incremental value of concentration-response (CR) over dose-response analysis (DR).

The objective of the current work was to compare the precision and accuracy of ED_{50} estimation directly through DR and indirectly through CR analyses in common dose-finding studies.

Methods

1) Simulation

Hypothetical drug response was simulated across different scenarios to investigate the impact of potentially relevant drug and design properties on imprecision and bias of ED_{50}.
Per scenario, 300 replicate parallel dose-ranging trials of 50 patients per trial were simulated.

- **Simulation assumptions**

- Direct Emax model as a function of steady state drug concentration (linear PK assumed).
- Log-normal between-subject variability on EC_{50}, Emax and CL/F.
- Proportional residual error in PD response.

- **Scenarios**

The following drug and design properties were chosen to mirror typical dose finding studies when drug efficacy is unknown and led to 486 scenarios.

- Between-subject variability (CV) on CL/F of 25, 50 or 75%
- Between-subject variability (CV) on Emax of 25, 50 or 75%
- Between-subject variability (CV) on EC_{50} of 25, 50 or 75%
- Residual error in PD response of 5, 15 or 25%
- A top dose (a hypothetical safety limit) of ED_{90}, ED_{70} or ED_{50}
- Three or six dose groups

Dose levels were multiples of ED_{50}, depending on top dose and number of dose groups.

2) Analysis

- CR or DR analysis, as appropriate, was conducted for each trial replicate.
- Population EC_{50} (for CR), ED_{50} (for DR), Emax and PD residual error were estimated.
- Between-subject variability was not estimated (one dose per subject).

3) Comparison of CR and DR analysis

- To allow CR/DR comparison, ED_{50} population estimate from CR was calculated as:

$ED_{50}=EC_{50}*CL/F$

where EC_{50} was the estimate from the CR analysis, and CL/F the geomean of simulated CL/F in the replicate.

- Imprecision (RMSE%) and bias (ME%) calculated for CR & DR analyses per scenario (1):

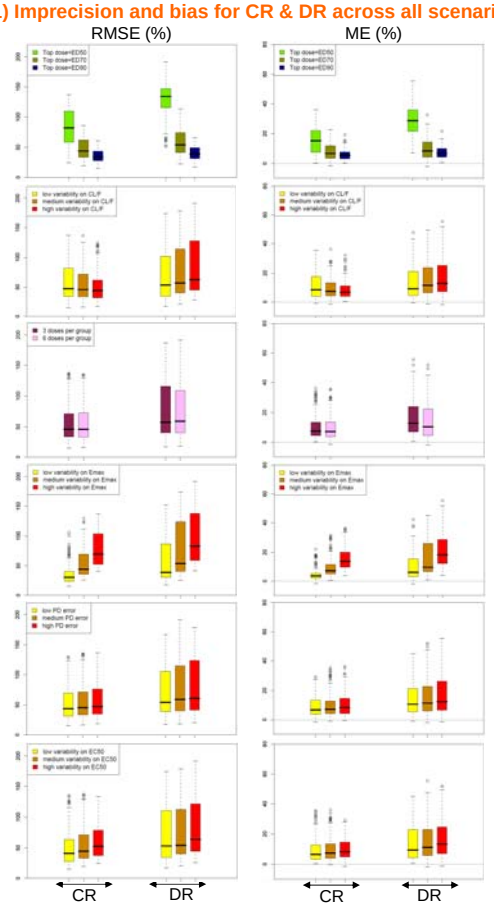
$$RMSE(\%)=\frac{\sqrt{\sum_{k=1}^{N=300}(\theta_k-\theta_T)^2}}{\theta_T}\times 100 \qquad ME(\%)=\frac{\sum_{k=1}^{N=300}(\theta_k-\theta_T)}{N\times\theta_T}\times 100$$

where:
- *k is the k^{th} simulated dataset [1-300]*
- *θ_k is the parameter estimate*
- *θ_T is the true parameter value*

- Differences in RMSE% and in ME% between CR and DR were calculated to assess the added value of CR over DR analysis.

Results

1) Imprecision and bias for CR & DR across all scenarios



- For RMSE:

- Factors with impact for CR: top dose, variability on Emax and variability on EC_{50}.
- Factors with impact for DR: top dose, variability on CL/F, variability on Emax and variability on EC_{50}.

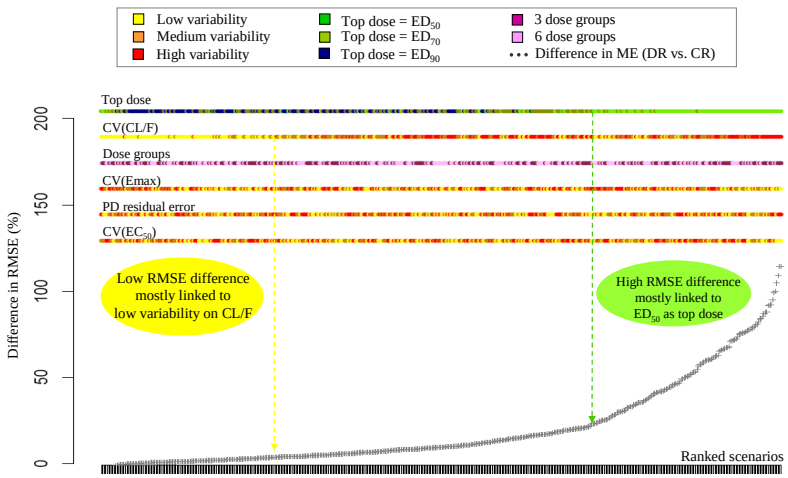
- For ME

- Factors with impact for CR: top dose, variability on Emax and variability on EC_{50} (small).
- Factors with impact for DR: top dose, variability on CL/F, dose groups, variability on Emax, and variability on EC_{50}.

2) Quantification of the incremental value of CR over DR (50 patients per trial)

- When the RMSE/ME difference between DR and CR is sorted in ascending order, a pattern of those drug or design properties that have a clear impact on such difference becomes apparent.

DR/CR difference in RMSE (same pattern observed for DR/CR difference in ME) :



- CR consistently out-performed DR with difference in RMSE and ME up to 100% and 40% respectively.
- Large difference between DR and CR (from ~25% to ~110% for RMSE and from ~10% to ~40% for ME) was almost all linked to top dose being less than ED70. Conversely, small difference (up to 5% for RMSE and ME) was mostly linked to CL/F variability less than 50%.
- The difference in ME and RMSE between CR and DR was less sensitive to the dose groups, the variability in Emax, the PD residual error and the variability in EC_{50}.

Discussion/Conclusions

- For all scenarios investigated here, CR consistently out-performs DR in ED_{50} estimate precision and accuracy.
- In the context of a parallel design (n=50) with a direct Emax model, the top dose is the only factor which consistently differentiated CR from DR in terms of RMSE and ME (up to 110% for RMSE and 40% for ME).
- These preliminary results are limited to a specific design and model. Further investigations such as cross-over design or more complex model need to be investigated.
- This project forms a simulation frame work for assessing the value added by PKPD analysis in ED_{50} estimation. It does not address the other advantages of having a CR approach like the time inclusion in PD response.

References (1) Dansirikul et al, J Pharmacokinet Pharmacodyn , Vol. 35, No. 3, 2008

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