Seeking ethically attractive dose-finding designs for narrow therapeutic index drugs

Rocío Lledó-García, Stefanie Hennig, Joakim Nyberg, Andrew C. Hooker and Mats O. Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background and Objective

Recently, a simulation-based comparison study on the relative merits of dose control-trials (DCT) with exposure-response analysis versus concentration control-trials (CCT) for drugs with expected narrow therapeutic index was performed[1]. Contrary to what had been suggested,[2, 3] it was shown that when learning about the exposure-response relationship, a DCT design is more informative than a CCT.

Herein, we revisit the question employing optimal design methodology, and propose strategies for designing ethically attractive trials for these drugs, which are balancing between individual risk, collective risk and informativeness.

Methods

PKPD model: The optimization was performed using PopED v.2.0 (http://poped.sourceforge.net/) considering a hypothetical immunosuppressant agent with two clinical endpoints (rejections and infections). The PK-model was described by the following equations: $AUC_i = \frac{D_i}{CL_i}$ $CL_i = \theta_{CL} \cdot e^{\eta_{CL}}$

and the PD-relationship with two independent logistic regression models (Figure 1).

$$P_X = \frac{e^{Logit_i}}{1+e^{Logit_i}} \quad Logit_i = \theta_{B_X} + \theta_{S_X} \cdot AUC_i \quad \text{X=infection, rejection}$$

Design setup: Parameter values were: θ_{CL} =20 L/h (45% BSV), θ_{Binf}= -3.5, θ_{Sinf} =15, θ_{Brej}= -1 and θ_{Srej}= -12. Clinical seriousness of rejection and infection episodes were considered equal. The optimization focused on estimating the PD parameters.

Different scenarios were optimized applying cost-based designs (Table 1) for 2 randomized, cross-over designs with (i) two dose levels as targets (DCT) and (ii) two exposures that reflect the expected average exposure in the corresponding DCT (CCT). The variables in the design which were simultaneously optimized were dose/exposure targets and number of subjects to include in the trial or in each arm.

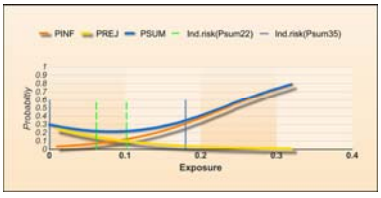

Figure 1. *PKPD relationship and dose/exposure levels limiting the surface area for a Psum 22% and Psum 35%*

Table 1. *A total of 40 scenarios were studied, considering different restrictions. All scenarios were investigates both with equally an unequally sized arms. The incorporation of prior information was also assessed.*

N subjects	Total *n* unwanted events allowed to occur in the trial	Maximal individual risk (Psum) (*)	Other design variables
200	unlimited	-	Different/ equally sized arms
unlimited	60	-	
unlimited	30	Psum: 22, 25, 30 35%	Prior/no prior information in baselines
200	unlimited	Psum: 22, 25, 30 35%	

(*) The individual risk or the probability of having an unwanted event (Psum) was translated into doses/exposures limits for DCT and CCT, respectively (Figure 1).

Sensitivity function: In the PD parameters no variability is present and therefore we optimize on a simplified criterion based on the sensitivity function of the model with respect to the parameters:

$$OFV = \left| \frac{\partial P_x}{\partial \theta} \cdot \frac{\partial P_x}{\partial \theta^T} \right|$$

Results and Discussion

Under restrictions of 200 subjects or total number of events (n=60) for equally sized arms, a placebo arm was found to be optimal in both the DCT and CCT. However, the higher dose/concentration differs between the two design types, being higher for the CCT (Figure 2). DCT was more informative as indicated by the sensitivity function. By treating each event, rather than a patient as the main cost of the trial, an almost equally informative trial, with lower number of events was achieved. However, with either of these constraints the lower optimal dose was close to zero, which is clearly ethically unacceptable for these particular class of drugs.

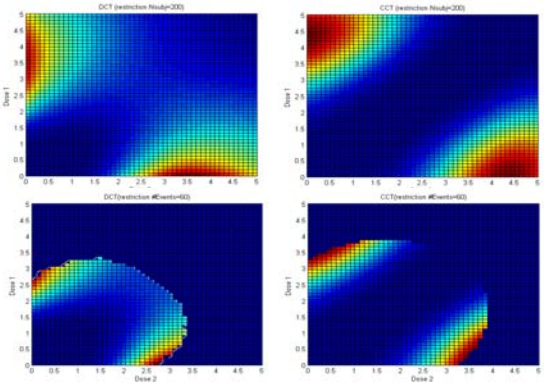

Figure 2. *Two-dimensional plots of the informativeness of different target dose combinations for DCT and exposures (for ease of comparison translated into typical doses through multiplication with the typical CL value (20 L/h)) for CCT, when the restriction of the cost was 200 subjects (top panels) or 60 number of events (bottom panels). The more informative the design, i.e. the higher the sensitivity, the more red the color of the area.*

A restriction on the Psum leads to DCT being more informative than the CCT with less cost, for all studied scenarios. The gain in information increases as the Psum increases and less numbers of subjects are recruited. To make the DCT Psum≤22% as informative as the Psum<35% by increasing its size, one would need to enrol 165 patients and have an expected number of events of 40, compared to the 98 patients. Thus, limiting the individual risk will be associated with the necessity of running a larger trial with an overall higher number of unwanted events to reach the same information about the dose-response relationship.

The prior information clustered both the higher and lower optimal targets closer to the optimal dose. It considerably diminishes the costs of gaining new knowledge, translated into a reduction in the total number of unwanted events/trial.

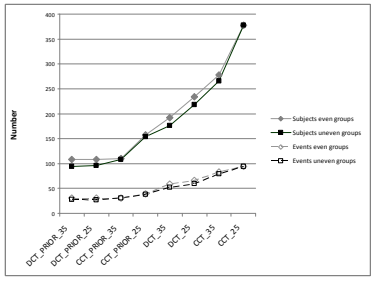

Figure 4. *Number of patients or events (y-axes) that provide the same value of |OFV| under optimal designs, given different design constraints (DCT or CCT, with or without prior information and different constraints on Psum (≤25% or ≤35 %)).*

To compare the informativeness between designs given different constraints, trials sizes were varied until all provided the same value for the sensitivity function (Figure 3).

Here it is shown that: i) DCT is more informative; ii) prior information translates into smaller trials with fewer expected number of events; iii) a small gain was seen when relaxing the assumption of having equally sized arms, but this gain is not reflected in a lower number of events and iv) constraining the Psum to higher levels leads to more informative designs. However, when prior information is utilized, the difference between trials with high and low individual risk is small for CCTs and absent for DCTs.

Conclusion

It was found that: (i) when exploring a wider range of possible designs, a DCT is more informative than a corresponding CCT, (ii) designs for which the cost is based on number of events can be equally informative and result in fewer unwanted events compared to designs which base cost on number of subjects, (iii) the quantitative trade-off between individual risk and number of events for a given amount of information about exposure-response can be mapped and may form a decision basis in designing trials, and (iv) the use of prior information on baseline frequencies of events can lead to considerably more informative and ethically attractive designs.

Reference

1. Lledó-García, R. et al. Clin Pharm Therapeutics, 2009.
2. Endrenyi, L. and J. Zha. Clin Pharmacol Ther, 1994. 56(3): p. 331-8.
3. Sanathanan, L.P. and C.C. Peck. Control Clin Trials, 1991. 12(6): p. 780-94.