Randomised dose controlled trials or concentration controlled trials when learning about drugs with narrow therapeutic windows?

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Background and Objective

Over the last two decades many comparisons between randomised dose controlled trials (DCT) and concentration controlled trials (CCT) have been made[1-3].

Interestingly, none of these has focused on the relative merits of CCT versus DCT for drugs with narrow therapeutic index, when considering the pharmacokinetic (PK) information in the exposure-response analysis for the DCT. This study aims at making such a comparison, for a more informative decision making assessing the possible gains and pitfalls of the trial designs.

Methods

PKPD model: A simulation-based study was performed using NONMEM VI considering a hypothetical immunosuppressant agent with two clinical endpoints (rejections and infections). The PK-model was described by equations: $C_i = \frac{D_i}{CL_i}$ $CL_i = \theta_{CL} \cdot e^{\eta_{CL}}$

and the PD-relationship with two independent regression logistic models (Figure 1). $Logit_i = \theta_{B_X} + \theta_{S_X} \cdot C_i$ $P_X = \frac{e^{Logit_i}}{1 + e^{Logit_i}}$ X=infection, rejection

Simulation setup: considered as typical value for clearance (θ_{CL}), 20 L/h and 45% of IIV. As baselines and slopes: θ_{Binf}= -3.5, θ_{Sinf} =15, θ_{Brej}= -1 and θ_{Srej}= -12. For illustration purposes, clinical seriousness of rejection and infection episodes are considered equal.

Study design: 3 randomized, cross-over designs with two dose/exposure levels were considered: (i) DCT with two dose levels as targets; (ii) TCCT (Target-equivalent CCT), with exposures that reflect the expected average exposure in the corresponding DCT; (iii) VCCT (Variance-equivalent CCT), targeting two exposure levels that results in the same total variability in exposure as the corresponding DCT.

Different study sizes and four different ranges of target levels were explored (Table 1). Considering the outcomes from the different scenarios the relative benefits of performing TDM versus a fixed dose regimen was assessed.

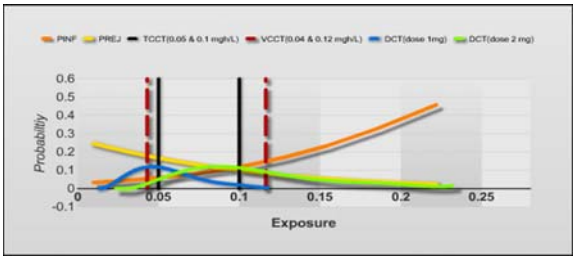

Figure 1. *PKPD relationship and dose/exposure levels corresponding to the adequate range for DCT, TCCT & VCCT*

Table 1. *Dose/exposure target levels for the different ranges explored. Both levels below, above, above but close or both levels on either side of the optimal exposure (0.08 mgh/L).*

Dose ranges	DCT		VCCT		TCCT	
	Dose (mg)		AUC (mgh/L)		AUC (mgh/L)	
Low	0.5	1	0.02	0.06	0.025	0.05
Close	1	1.5	0.041	0.091	0.05	0.075
Adequate	1	2	0.043	0.116	0.05	0.1
Above	2	4	0.086	0.233	0.1	0.2

Results and Discussion

The DCT was superior over both CCTs in all the following respects: (i) precision and bias in parameter estimates (Figure 2), (ii) precision and bias in the estimate of optimal exposure, (iii) bias in prediction of the therapeutic benefit at estimated optimal exposure (Figure 3), and (iv) bias in prediction of the therapeutic benefit of dose individualization over fixed dosing (Figure 4). This superiority was evident across all study sizes and target ranges explored.

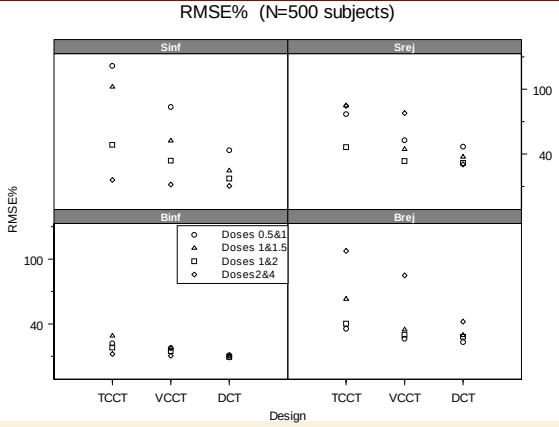

Figure 2. *The RMSE % for the estimated θ_{Binf}, θ_{Sinf}, θ_{Brej}, θ_{Srej} is shown for DCT, TCCT and VCCT (at the different ranges of the studies)*

(i) There is a gain in information regarding the exposure-response surface when performing a DCT over CCTs. The improvement in parameter precision inherently leads to a better decision making with regards to the optimal dose/exposure to be applied in future studies.

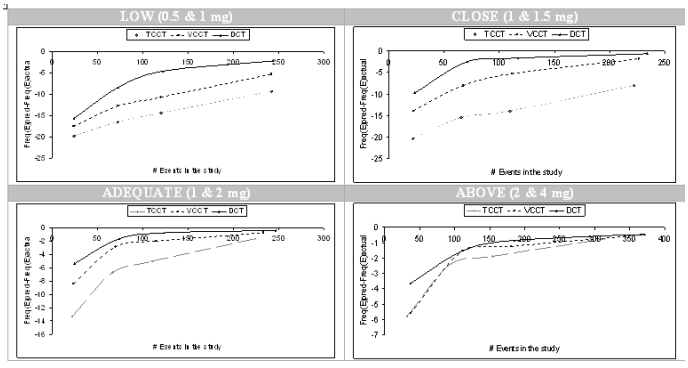

Figure 3. *The difference between the predicted frequency of events (%Freq(E)pred) and the actual frequency of events (%Freq(E)actual) for a target population at estimated optimal exposure versus the number of events in the clinical trial*

(iii) Figure 3 shows more marked under predictions in the frequency of events for CCTs, leading to an overoptimistic view on therapeutic benefit.

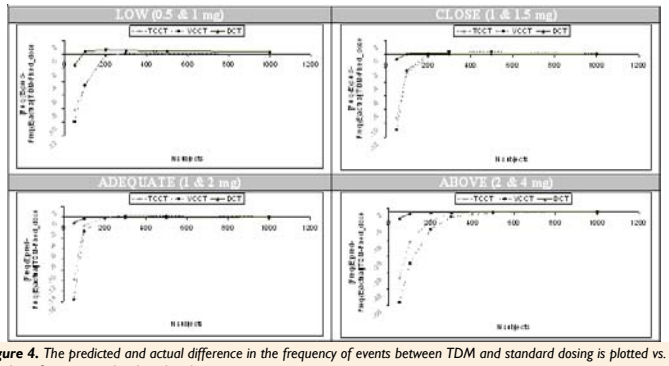

Figure 4. *The predicted and actual difference in the frequency of events between TDM and standard dosing is plotted vs. the number of patients in the clinical trial.*

(iv) Figure 4 shows that CCT are overoptimistic in the gain that can result from TDM compared to fixed dose regimens.

Conclusion

A DCT design is more informative when describing the exposure-response relationship for narrow therapeutic index drugs. It will provide more information on parameters, the optimal dose and improve prediction of the expectations of adverse events in the target population. The DCT can reach the same parameter precision with a lower number of subjects and with fewer adverse events in the dose-finding study

Acknowledgments

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Reference

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