Assessing the Propagation of CYP2C9 polymorphisms into the PK/PD of *(S)*-warfarin using Clinical Trial Simulations (CTS)

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BACKGROUND

- *(S)*-warfarin (S-WRF) is metabolised by the polymorphic enzyme, cytochrome P450 2C9 (CYP2C9).
- Several studies have assessed the impact of genetic variations in *CYP2C9* on the pharmaco-kinetics (PK) of S-WRF (Table 1) and its pharmacodynamics (PD) with respect to therapeutic response and maintenance dose requirements (Table 1).
- However, while some studies have demonstrated significant differences in the PK or PD of S-WRF between the wild type genotype and various other genotypes, the results have not been consistent across the studies.
- Although clinical trial simulations (CTS) might be used to evaluate some of the above issues, the current examples rely on data collected from preliminary clinical studies and may not be applied at earlier stages of drug development.

AIMS & OBJECTIVES

- To use mechanistic-based CTS as a tool to investigate the influence of *CYP2C9* genotype on S-WRF PK and PD by extrapolating known information on its *in vitro* metabolism to *in vivo* clearance.
- To assess the effect of sample size on the power of studies to detect differences in S-WRF PK and PD between different *CYP2C9* genotypes.

METHODS

- A meta-analysis was conducted to assess the activity of *CYP2C9* genotypes relative to the wild type from *in vitro* data[1-5] (Fig 1.). The genotype frequencies were taken from the literature[6] (Fig 1.).
- The above information and the *in vitro* metabolic data, were entered into Simcyp® algorithms (www.simcyp.com), which also account for other physiological and demographic features. The simulated population PK of S-WRF in the different genotypes (Fig. 2) was then integrated into a PK/PD model derived from *in vivo* studies[7].
- S-WRF concentration- and effect (anticoagulation) - time profiles were simulated for each individual in a population using different study sizes (n = 10 to 550).
- Twenty clinical trial simulations were carried out for each n value. The percentage of trials showing a significant difference between *CYP2C9* genotypes (ANOVA) was taken as the power of that particular simulation.
- The sensitivity of study power to various aspects of study design including the effects of 'enrichment' and 'biomarker (INR) related dose adjustment' were investigated.

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Frequency and Relative Activity of *CYP2C9* Genotypes

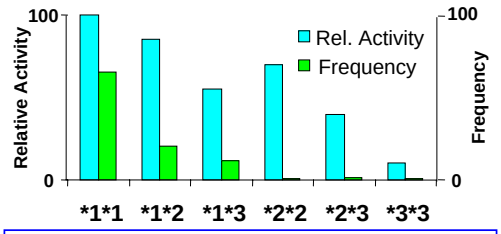

Figure 1: The frequency and relative enzyme activity of *CYP2C9* genotypes, derived from a meta-analysis of the literature[1-6].

Schematic Representation of the IVIVE Model

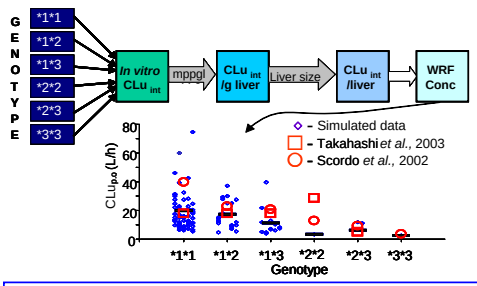

Figure 2: Schematic representation of the model for propagating genetic variation in *CYP2C9* activity into S-WRF clearance. The trend in simulated values (blue) can be compared with mean experimental values (red) from reported studies.

Graphs of Study Size *vs*. Study Power

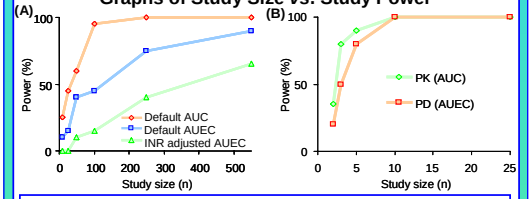

Figure 3: Study size and power to show a significant difference in AUC or AUEC between (A) the wild type and a combination of other genotypes using either default or INR adjusted dosage conditions; and (B) wild type and the *3*3 genotype using enriched recruitment conditions.

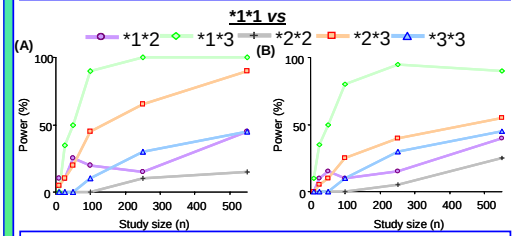

Figure 4: Study size and power to show a significant difference in (A) AUC or (B) AUEC between each single non-wild type genotype and the wild type genotype

Table 1: Observed outcome (✓ or ×) and predicted power (% likelihood) are indicated. Colour code shows consistency (green) or inconsistency (red) between predictions and observations.

			Significant relationship between *1/*1 *vs.*											
Reference	PK or PD?	n	*1/*2		*2/*2		*1/*3		*2/*3		*3/*3		Comb	
Takahashi *et al.*, 2003[8]	PK	47	×	25	×	0	×	48	×	20	×	0		
Scordo *et al.*, 2002[9]	PK	93	×	20	×	0	×	82	✓	44	✓	10		
Kamali *et al.*, 2004[10]	PK	121	✓	20	×	0	×	92	×	48	×	12		
Loebstein *et al.*, 2001[11]	PK	156	×	18	×	0	✓	94	×	52	×	16		
Takahashi *et al.*, 2003[8]	PD	47	×	15	×	0	✓	48	×	15	×	0		
Khan *et al.*, 2004[12]	PD	53	×	16	×	0	✓	50	×	16	×	0		
Joffe *et al.*, 2004[13]	PD	73	×	12	×	0	✓	64	×	26	×	4	✓	42
Scordo *et al.*, 2002[9]	PD	93	×	10	×	0	✓	76	✓	45	✓	10		
Kamali *et al.*, 2004[10]	PD	121	×	10	×	2	✓	82	×	45	×	12		
Siguret *et al.*, 2004[14]	PD	126	×	11	×	2	×	82	×	45	×	13		
Loebstein *et al.*, 2001[11]	PD	156	✓	12	×	3	✓	86	×	45	×	16		
Tabrizi *et al.*, 2002[15]	PD	153	✓	12	×	3	✓	86	×	45	×	17		
King *et al.*, 2004[16]	PD	159	×	12	×	3	✓	88	×	45	×	18		
Peyvandi *et al.*, 2004[17]	PD	175	×	12	×	3	✓	88	×	45	×	20	✓	60
Maragaglione *et al.*, 2002[18]	PD	180	✓	12	×	3	✓	88	×	45	×	20		
Higashi *et al.*, 2002[19]	PD	185	×	12	×	3	×	90	×	45	×	21	✓	62
Lindh *et al.*, 2005[20]	PD	219	×	14	×	4	×	92	×	45	×	26	✓	68
Sconce *et al.*, 2005[21]	PD	297	✓	20	✓	8	✓	94	×	50	×	32	✓	78
Aquilante *et al.*, 2006[22]	PD	350	×	24	×	12	×	94	×	54	×	35	✓	80

RESULTS

- Figure 3 (A) shows the power to detect differences in the area under the concentration - time curve (AUC) between wild type (*1*1) and a 'combination' of the other genotypes as a function of study size. The power to detect differences between the wild-type and any other single genotype is shown in Figure 4 (A).
- Figures 3 (A) and 4 (B) show the corresponding powers for differences in the area under the effect – time curve (AUEC).
- Figure 3 (A) also shows the effect of INR related dosage adjustment on the power to differentiate the AUEC of S-WRF between the wild-type and a combination of any other genotype.
- Figure 3 (B) shows the effect of 'enrichment' on study power.
- Table 1 is a summary of the results of the published studies and their predicted powers. There was good overall concordance between the predicted and observed percentage of studies successful in differentiating (S)-warfarin PK or PD between the wild type and any single other genotype (20% *vs*. 21%; p value of 0.8 from Chi square).

DISCUSSION

- The predicted clearance associated with different genotypes (using *in vitro* data) were consistent with those reported in experimental studies (Fig. 2).
- The model projection indicated that at least 90 subjects would be required to detect a difference (80% power) in the AUC of S-WRF between wild genotype and the combination of all other genotypes (Fig. 3 A). The corresponding number to detect differences in AUEC of S-WRF was 250 subjects (Fig. 3 A).
- Comparisons between the wild type and specific genotypes would require much higher number of subjects (e.g. 420 subjects to achieve 80% power in discriminating PK between wild-type and *2/*3 under the 'uniform dosage' condition; Fig. 4).
- The predicted powers were consistent with the reported observations (Table 1).
- When biomarker related dose adjustment was simulated, the power to detect differences in the PK and PD of S-WRF between the wild type and a combination of any other genotype was much lower (Fig. 3A)
- This indicates that the use of INR as a biomarker to adjust the dose of (S)-warfarin, should preclude major difference in therapeutic response between genotypes under long term use of the drug.
- The 'enriched recruitment' design requires a very small number of subjects to separate genotypes with respect to both PK and PD differences (Fig. 3B). However, this will require prior screening of many individuals in order to find the rare genotypes.

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