Quantitative Approach for Cardiac Risk Assessment and Interpretation in Tuberculosis Drug Development

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Introduction

Cardiovascular toxicity is one of the leading causes of early and late attrition during the drug development process, as well as a major contributor to withdrawals of marketed drugs. Cardiac safety concerns arise from a variety of mechanisms, including direct myocyte injury, activation of apoptotic and necrotic changes, alternation of ion homeostasis or the signaling pathways or influence on the transcription factors i.e. kinase inhibitors. Cardiac arrhtyhmia is one of the most frequent cardiac safety liabilities responsible for toxic effect, often recognized in the late stage of clinical development and during post-marketing surveillance. Torsade de Pointes (TdP) is a syndrome of polymorphic ventricular arrhythmia occurring in the setting of marked prolongation of the ECG QT interval. Such cardiac safety risks have led to the withdrawal of many approved drugs from the market and is a leading cause of drug attrition during development. The recently approved drugs for multi-drug resistant pulmonary tuberculosis (e.g. bedaquiline) tend to influence parameters which may be pro-arrhythmic. Therefore algorithms for the drug-related cardiac risk assessment are needed.

Objective

The aim of the current work was to develop the in silico-based models for the early prediction of the cardiac risk propensity with the use an in vitro to in vivo extrapolation (IVIVE) approach. One of the assumptions was to develop systems which can be utilized at various stages of the drug devlopment, and therefore working on different set of available information.

Materials and Methods

There were two different approaches applied during the models development as presented below on Figure 1.

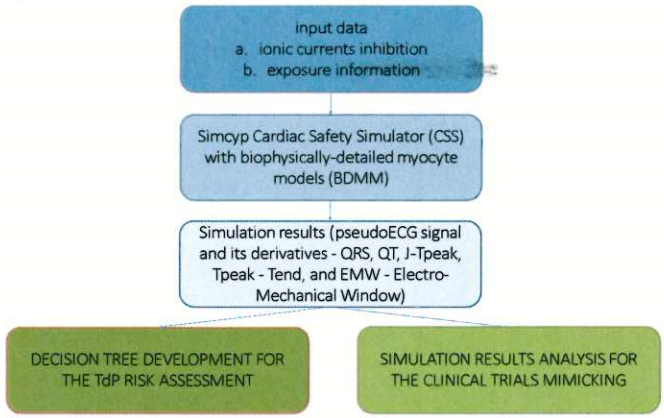

Figure 1. Two approaches applied for the models development.

Biophysically detailed computational models (BDMD) of cardiomyocytes in combination with appropriate in vitro cardiac ion channel inhibition data of the drug has recently been identified as a potentially efficient and economic approach to identify the arrhythmic risk and in turn reduce or avoid clinical studies

The Simcyp Cardiac Safety Simulator (CSS) with biophysically-detailed myocyte models (BDMM) describing electrophysiology of the human left ventricular cardiomyocytes was utilized. The input data include:

A. ionic channel inhibitory effects as measured by patch clamp assay (e.g., IC50 values for IKr, IKs, INa, ICa and other currents if available in the literature),

B. drug concentrations of parent and/or active metabolites obtained from clinical studies or simulated using PBPK models such as Simcyp, and individual subject covariates.

Simulation results (pseudoECG signal and its derivatives - QRS, QT, J-Tpeak, Tpeak - Tend, and EMW - Electro-Mechanical Window) were used to either develop empirical classifiers or directly to assess cardiac clinical consequences by mimicking the clinical trials.

Main references

Dooley et al.. 2012 J Acquir Immune Defic Syndr 2012;59:455–462.

FDA. Center for Drug Evaluation and Research, Application Number: 204384Orig1s000, Pharmacology Review(s) http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/204384Orig1s000PharmR.pdf .

Glinka A, Polak S. Toxicology Mechanisms and Methods, 2015; 25(4): 279-286.

Jamei M. et al. In Silico Pharmacol. 2013 Jun 3;1:9. doi: 10.1186/2193-9616-1-9.

Materials and Methods cont.

The empirical classifiers were built with the use of decision trees algorithms with 96 drugs used as the learning dataset. 9 active concentrations were tested (0, 0.0001, 0.001, 0.01, 0.1, 1, 10, 100, 500 µM). The simulated endpoint which was assumed to be the surrogate of the drugs proarrhythmic potency was defined as the iCEB (index of cardiac electrophysiological balance, where iCEB = QT/QRS). 12 known drugs, 6 TdP+ (Amiodarone, Citalopram, Clarithromycin, Dofetilide, Moxifloxacin, Quinidine) and 6 TdP- (Fexofenadine, Propafenone, Verapamil, Hydrodolasetron, Ranolazine, Vardenafil) were chosen as the validation dataset. 2 anti-TB drugs (Bedaquiline, Moxifloxacin) were tested.

For the simulations mimicking clinical results free plasma concentration was assumed to be the active fraction surrogate. In opposite to the above described empirical model development, here whenever possible known active metabolites (i.e. dolasetron-hydrodolasetron, quinidine - 3-OH quinidine) were also accounted for. The simulated/calculated endpoints were supposed to mimic those originally reported in the original scientific report derived from the literature.

Results and Discussion

The most robust empirical model built with the use of alternative decision tree (Adtree – Figure 2) algorithm, utilizing electromechanical window (EMW) and iCEB was able to correctly classify 85 out of 96 records during the internal validation step (89% of accuracy), and 10 out of 12 (citalopram and quinidine classified incorrectly) external validation compound (83% of accuracy) for their TdP propensity (Figure 3).

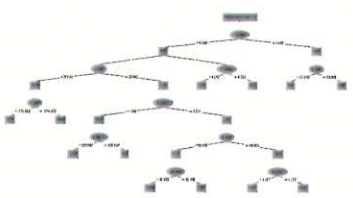

Figure 2. Decision tree structure.

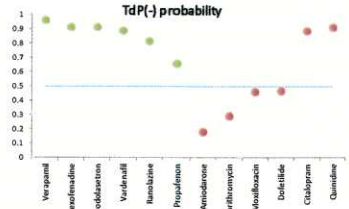

Figure 3. Validation dataset prediction.

During the population simulation, the final endpoints depended on those reported in the original works. Regardless of the endpoint, the obtained results matched well the clinical observations in all cases. The input data included the literature derived, in vitro measured ionic currents inhibition for bedaquiline and its main metabolite M2 (Table 1).

	TMC207			M2		
	IC50 (mcM)	model	n	IC50 (mcM)	model	n
IKr	0.37 (0.2 mcg/mL)	HEK29	3	0.45 (0.24 mcg/mL)		
IKr	0.2 mcg/mL		0.7	0.2 mcg/mL		
IKr					HEK29	
					0.923	0.99
IKs	up tp 32% starting from 0.003 mcM			up to 37% starting from 0.3 mcM		

Table 1. In vitro measured ionic currents inhibition for bedaquiline and its main metabolite.

The exposure data were simulated with the use of Simcyp Simulator (V12.1) as presented on Figure 4.

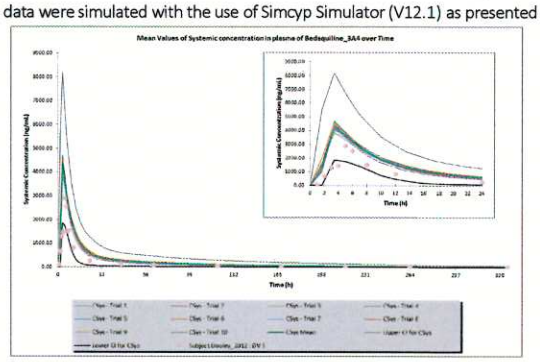

Figure 4. Individual concentration – time traces were simulated with the use of Simcyp Simulator and full PBPK model.

For bedaquiline the predicted vs observed QTcF (derived from the simulated ECG QT value corrected for the heart rate with the Fridericia algorithm, where QTcF = QT/RR1/3) values (ms) were: -4.1 vs -4.7 and 6.4 vs 3.8 for the 1st and 7th day of treatment respectively.

Results and Discussion

An in silico modelling and simulation approach that considered ECG changes beyond QT was proposed as a tool for the drugs and drugs combination cardiac safety assessment. This approach allows for the early screening as well as testing of clinical scenarios.