Use of Secondary Intelligence™ to predict QTc interval prolongation in humans from hERG margin data

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Background

The Thorough QT/QT_c Study (TQTS) remains at the core of the QTc regulatory guidance[1]. It is conducted in late development and is deemed 'positive' if QT_c increases by ≥10 ms. However, an early development, PKPD study can be a TQTS alternative. Also, for many oncology drugs neither approach is feasible and only a relatively crude clinical QT_c risk assessment is conducted.

For these non-TQTS options, demonstration of a so-called 'double negative' non-clinical profile (hERG and in vivo QT_c) may be needed to confirm a low QT_c risk. Predicting the safety margin of new compounds relative to known QT_c prolonging drugs is therefore useful for all three clinical risk assessment scenarios.

Related to the regulatory guidance, a consensus within the pharma industry is that a compound has a low proarrhythmic risk if it is both 'hERG negative' and 'QT negative', and a ≥30-fold hERG margin has been proposed to define 'hERG negative'[2].

Secondary Intelligence™ is a new software tool built from quantitative analysis of (predominantly) marketed drugs selective for a given receptor. The analysis comprises plots of their pharmacodynamically effective unbound plasma concentration ($C_{eff\text{-}u}$) in humans divided by in vitro K_i or IC_{50}, for >60 off-target receptors, including hERG. The principle of Secondary Intelligence™ is that if the $C_{eff\text{-}u}/IC_{50}$ ratio of a test compound falls within the range of the reference drugs, then it is considered likely to produce their characteristic pharmacodynamic effects in clinical use, as an off-target adverse effect.

We applied the hERG tool in Secondary Intelligence™ to two sets of drugs, rated as either positive or negative in the TQTS, to ascertain whether it could predict the outcome.

Methods

The hERG plot was constructed using 9 Class III antiarrhythmics by curating $C_{eff\text{-}u}$ values associated with a 10 ms increase in QT_c interval divided by their published mean IC_{50} at hERG (Figure 1). All data were from manual or automated electrophysiology on hERG-transfected human cell lines. To assess whether SI would predict QT_c prolongation as a side effect, data on unbound Cmax plasma concentrations and IC_{50} at hERG were curated from drugs that were either classed as positive or negative in the Thorough QT Study (TQT-POS, n = 9; TQT-NEG, n = 7). The TQTS involves generation of high-quality ECG and pharmacokinetic data in healthy subjects under standardised protocols. Original publications curated in ToxPortal[2] were accessed for all the above data.

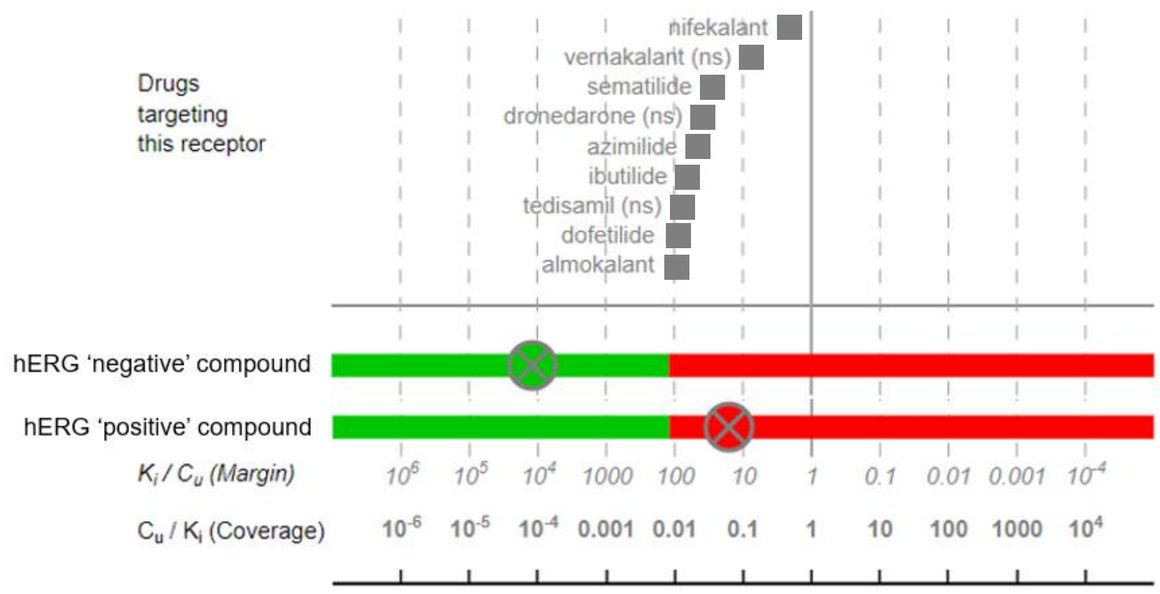

Figure 1. Plot of $C_{eff\text{-}u}$ (abbreviated to 'C_u' in the figure) divided by hERG IC_{50} for 9 Class III antiarrhythmic drugs, which target hERG block as their primary therapeutic mechanism. $C_{eff\text{-}u}$ in this case is the plasma concentration associated with a 10 ms increase in QT_c in humans. The principle in Secondary Intelligence is that if the same ratio for a test compound (using real or predicted $C_{max\text{-}u}$) falls within the range of the reference drugs, then it is considered highly likely that the characteristic pharmacodynamic effects of the reference drugs will be seen with the test compound in clinical use. The positions of the ratios for two test compounds are indicated by the circles.

Results

Secondary Intelligence™ correctly predicted QTc prolongation (>10 ms) for 8/9 drugs, and a lack of it for 4/7 drugs, indicating a sensitivity of 89% and a specificity of 57% (Figure 2).

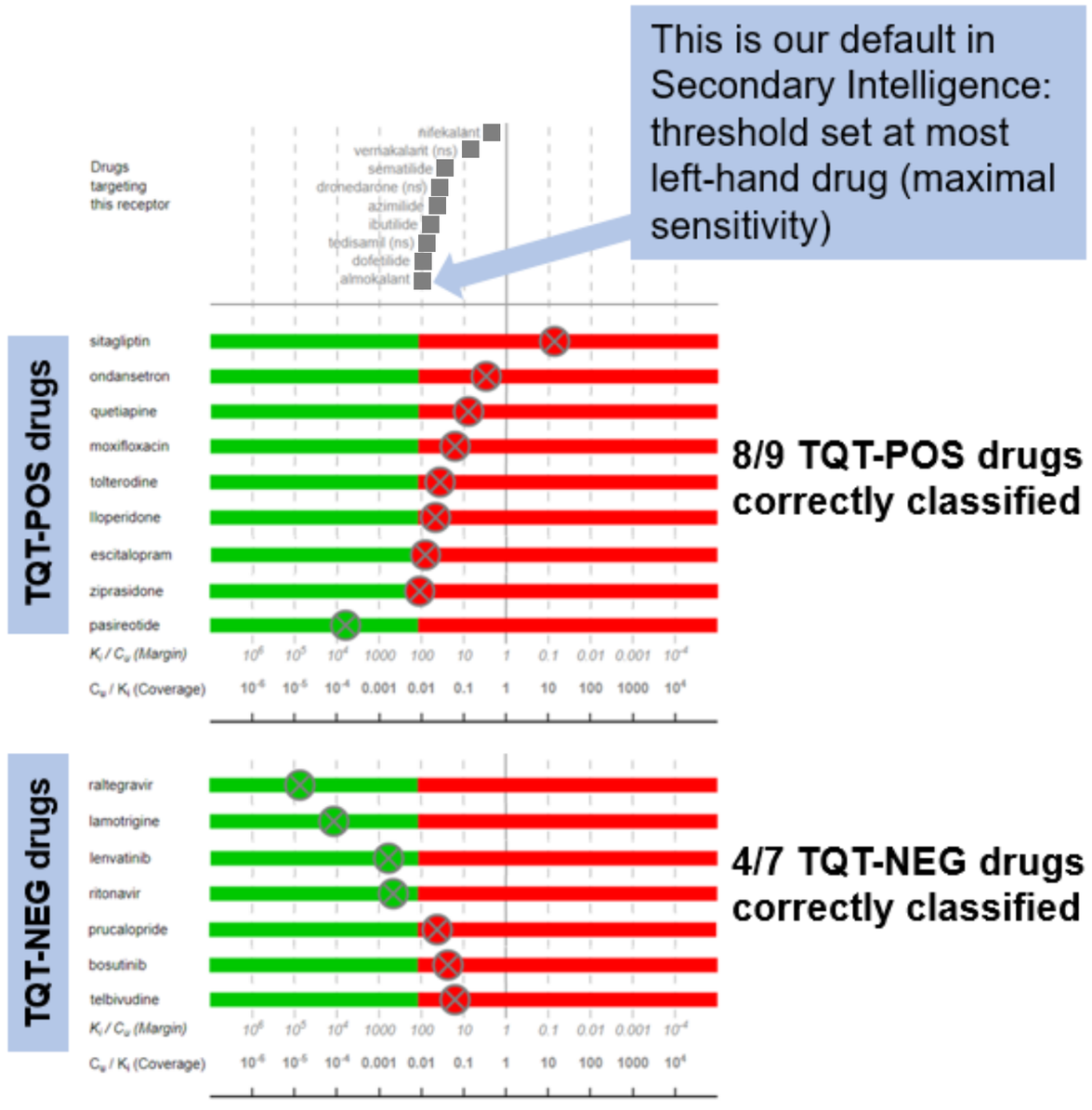

Figure 2. Use of the hERG 'classifier' in Secondary Intelligence™ correctly predicted 8/9 TQT-positive drugs and 4/7 TQT-negative drugs. The one 'false negative' (pasireotide) is a 1 kD MWt somatostatin analogue associated with bradycardia and hyperglycaemia, which may contribute to a non-hERG mechanism of QTc prolongation. The 3 'false positives' could potentially also block $Ca_V1.2$ which would offset the hERG block, but there are no published data on their activity at cardiac ion channels other than hERG.

Conclusions

This tool would be helpful in deciding what constitutes a 'hERG positive' outcome, thus providing an early indication of the need to plan for further risk assessment, including via CiPA work streams[2].

It can also be deployed to assess the level of risk of detecting QT_c prolongation in clinical studies, even prior to generating in vivo QT_c data in preclinical species.

In the specific case of oncology drugs (which do not require a TQT), a negative outcome in the hERG plot in Secondary Intelligence™ provides confidence that the candidate drug is safer than all the reference drugs (QT_c-prolonging Class III antiarrhythmics).

References

1. Anon. (2022) ICH guideline E14/S7B: Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential - questions and answers. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e14/s7b-clinical-nonclinical-evaluation-qt/qtc-interval-prolongation-proarrhythmic-potential-questions-answers-step-5_en.pdf

2. Vargas HM et al. (2020) Time for a fully integrated nonclinical–clinical risk assessment to streamline QT prolongation liability determinations: A pharma industry perspective. Clin Pharmacol Ther doi:10.1002/cpt.2029

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