EDITORIAL

The Thorough QT Study: Is Its Demise on the Horizon?

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In response to concerns regarding the public health implications of drugs being approved that have a proclivity to cause the potentially lethal ventricular arrhythmia torsade de pointes (TdP), there was an international regulatory call to action in 2001. This culminated in the 2005 International Committee on Harmonization (ICH) ICH E-14 guidance "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."[1,2] Since then, almost all new chemical entities with systemic exposure have undergone a dedicated study to determine the potential of the compound to prolong the QTc interval. A "positive finding" in this resource-intensive study can have a major impact on the remainder of a drug's development (e.g., extensive ECG assessments during phase 3, potential approval delays, etc.) and, in some cases, has resulted in termination of the development program.

The article by Darpo and colleagues[3] in this Journal details a prospective study to test the hypothesis that using PK/QTc modeling in a single ascending dose design study, such as is typically performed in the first-in-human study (FIM), will be sufficiently sensitive to detect QTc effects, to be acceptable in lieu of the thorough QT (TQT) study. Reasons to be optimistic that this important effort is likely to be successful include the fact that careful core-lab analyzed ECG assessments in phase 1 is an approach that is already being used by some pharmaceutical companies to make early determinations of the potential for QTc prolongation (AstraZeneca personal communication), and that the science underlying exposure-response modeling is robust.[4,5] More than 350 TQT studies have demonstrated that QTc interval prolongation, when present, is almost uniformly closely tied to plasma concentrations. PK/QTc modeling utilizes paired QTc and PK assessments regardless of dose, providing far greater power to observe (or exclude) a QTc signal than would be possible with the time-matched methodology that is the primary analysis approach used in TQT studies.

The potential of this effort to move the clinical and regulatory assessment of the potential for QTc prolongation from phase 2 to early in phase 1 assessment could beneficially impact drug development by identifying or excluding a potential cardiovascular (CV) safety issue earlier, thus saving resources expended on a stand-alone TQT study. In addition, early signal detection might result in refocusing the drug toward patients with greater potential benefit. However, as the authors point out, <10% of drugs undergoing FIM studies complete phase 3. Thus, companies will need to make decisions about the strategy for any individual drug, integrating preclinical ion channel, animal QT data, and toxicology data along with other CV safety items related to the chemical and drug class, to determine the adequacy of early QTc evaluation versus waiting to perform

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the TQT study later in development. Concerns about a potential QT effect or bringing forward a drug in a class that has had safety signals, would likely strongly favor the FIM PK/PD approach. The relative cost implications of the various ECG strategies, integrating different risk scenarios, would need to be considered. For example, some companies might choose to perform the FIM study using appropriately designed protocols that permit the collection of high quality ECG data, but only analyze the ECG data when it is clear that the drug does not have significant noncardiac toxicity or adverse events that could derail development.

There are several other issues that need to be further weighed. The PK/PD FIM approach as currently applied, does not assess assay sensitivity. It is not feasible to add an active control arm to a FIM study, and while statistical approaches can potentially be utilized to address this issue,[6] it remains to be seen if assay sensitivity is critical for the PK/PD approach to be used in lieu of the TQT study.

The study described by Darpo et al.[3] has more subjects per dose group (nine receiving active drug and six receiving placebo compared to six and two, respectively). However, this is mitigated by the fact that only two doses are studied and that a typical FIM study typically has ~5 dose groups. However, the PK/PD FIM approach may have reduced applicability for FIM studies that utilize smaller cohorts or fewer dose groups or those that do not truly explore supra-therapeutic exposures. Drugs with long half-lives may require multiple doses to reach sufficient exposures and this approach could be utilized in the multiple ascending dose study.

Finally, the FDA has been involved in the development of this experimental approach. In order for positive results to meaningfully impact drug development, it is critical that other regulatory authorities accept the new approach and that ICH-E14 be revised. Acceptance of the PK/PD approach in one region but not in another might not obviate the need for a TQT study in an individual drug development program.

The major weakness of using QTc prolongation to assess risk of TdP is that it does not directly address the most critical issue: is the drug actually proarrhythmic? A significant increase in the QTc is sensitive, but not highly specific for the development of TdP.[7] For example, ranolazine and phenobarbital prolong the QTc but are not associated with TdP. Amiodarone markedly increases the QTc (occasionally >550 ms), but it is only very rarely associated with TdP. Additionally, verapamil potentially blocks the human ether-a-go-go-related gene (hERG)-related current, the ionic effect most commonly associated with drug-induced proarrhythmia. However, verapamil does not prolong the QTc at therapeutic exposures. While all of these examples block hERG, they also modulate other cardiac ionic currents, which appear to prevent the proarrhythmic effects of hERG blockade and QTc prolongation. These and other examples illustrate that hERG block and QTc prolongation can be differentiated from TdP risk for some drugs. Since ICH E14 has been put into place in 2005, many drugs have prolonged the QTc above the threshold of regulatory concern and received labeling warning regarding QTc prolongation and the potential for cardiac proarrhythmia. How likely is it that many of these agents resulting in small QTc increases are actually proarrhythmic?

The current paradigm undoubtedly results in the premature discontinuation of drugs because of QTc prolongation and concerns of a perceived safety risk despite the real possibility that there is not a real proarrhythmic risk.[8] The costs and complexity of developing a drug with a "QTc signal" is burdensome with real concerns regarding labeling with arrhythmia warnings. The net result is that drugs that could have conceivably addressed unmet medical needs and had positive benefit: risk ratios, are being prematurely terminated.

Given this issue, the Cardiac Safety Research Consortium (CSRC), in conjunction with the Health and Environmental Sciences Institute (HESI) and the FDA held a Think Tank on July 23, 2013 at the FDA to critically discuss a new paradigm to directly evaluate the potential for a drug to be proarrhythmic. The focus would be on nonclinical proarrhythmic assays and the goal would be to reduce the premature termination of drugs that effect hERG or increase the QTc but do not appear to be proarrhythmic. This would effectively move the bulk of proarrhythmia signal detection to the discovery phase, where the assays could potentially play a role in candidate selection, and obviate the TQT.[9] Collaborative work streams are now being put into place to perform the necessary work.

Specific efforts are concentrated on assessing the effect of a drug on a platform of ion channels using in silico techniques[10] to assess the proarrhythmic potential. The proclivity to develop early after

depolarizations and enhanced susceptibility of ventricular depolarization during the repolarization phase are being studied. Conceivably, the results could be confirmed in a human myocyte study, potentially using induced pluripotent stem cells.[11] ECG assessment in phase 1 will still be important. It will be critical to determine whether there are findings in humans that were not anticipated based on the nonclinical assays (and thus the mechanism would need to be understood) as well as the effects of a drug on other important ECG variables such as atrioventricular nodal conduction, ventricular conduction, heart rate, and possibly T-wave morphology.

This is an exciting time. Initiatives such as FIM PK/PD assessments in lieu of the TQT and the new preclinical paradigm could conceivably move the bulk of proarrhythmia assessment to the discovery phase. It has the potential to make drug development more efficient and significantly reduce the number of cases in which there is a need for the TQT study. We anxiously await the results of the study described by Darpo et al.[3] and the efforts of the work-streams focused on the developing a new approach to the assessment of proarrhythmia risk.

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