Emerging approaches to assess proarrhythmic risk: *Regulatory perspective*

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Introduction

About 15 years ago, there arose great concern that we approved and then removed from marketing a number of drugs (6 in US) with an under-appreciated risk of TdP. The centerpiece of the regulatory response was ICH E14, which based a clean bill of health upon the exclusion of an effect on QT as large as about 3%. Little evidence supported this threshold; it was based in extreme risk aversion.

Success

- No drugs removed from the market for proarrhythmic risk after 2001.
- Lots of effort expended on …
  - Design
  - Conduct
  - Analysis

… to make “Thorough QT” studies as efficient as possible

Exposure-response

- Another step in evolution of getting QT data efficiently
- Drug effects seldom show hysteresis
- Abundant anecdotal evidence that early phase studies—often with highest exposure—could provide information equivalent to a separate TQT study

E-R: Regulatory response

- Prospective IQ/CSRC study (Keirns poster)
  - 5 drugs with modest effects
  - (1 negative control)
- ICH E14 Discussion Group
  - More systematic review of retrospective examples
    - Several pharma cohorts
    - FDA analysis of last 30 TQT studies
  - Likely incorporation of this option as an alternative to standard TQT

E-R: Regulatory response

- Standard TQT has built-in positive control—moxifloxacin—which allows innovation
- Desire not to further burden early phase studies, so community effort now ongoing to see if there are features in the ECG data that can provide confidence that a negative result is interpretable.

Cost

- Few $M to do a TQT study. Given the low positive rate, is this efficient?
  - Improved by embedding in early phase
- Cost of false positive errors probably dwarfs the $B spent on TQT studies
  - Labeling that conveys concern when there ought be none
  - Drug development aborted because of hERG effects or QT effects

CiPA

- Address false positive problem through a mechanistic assay
- No gold standard—so how do you validate?
  - Scientific consensus
  - Reference compounds
- What else do you need?
  - Curation
  - Attitude

CiPA validation: consensus

- Series of meetings of experts beginning in 2012
- Series of public presentations since 2013

- Results: Concerns about all kinds of details, but no fundamental problem with the general concept of an assay based on our current mechanistic understanding of these arrhythmias.

CiPA validation: reference set

- Validation or calibration?
- There is no problem counting arrhythmia cases on drugs, but a big problem sorting out how much of the picture is a fundamental property of the drug and how much is attributable to population risks.
- Initial efforts to develop 5-category assignment collapsed into 3 risk categories—and there are differences in expert opinions there, too.

CiPA what else: curation

- Progress on engineering the TQT was possible through ECG Warehouse, systematic collection of TQT study results, and collaborative environment
- For CiPA, we plan to collect voltage clamp data, maintain the in silico model, and perhaps collect the myocyte results.

CiPA what else: attitude

- CiPA seeks to “fix” something that is “working”.
- False negatives not expected to be common, but one has to be willing to accept more risk initially, to put systems in place for detecting and correcting problems efficiently

Summary

Regulatory agencies have been partners with regulated industry for development of strategies to address the proarrhythmic potential of drugs, and that partnership continues with current initiatives.

Our shared mission needs to be to seek the right balance between risks of approving drugs with proarrhythmic potential and of constricting the drug development pipeline.