An Industry Perspective on the Assessment of Pro-Arrhythmic Risk of New Drug Candidates

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COI & Disclaimer

- I am employed by Astellas Pharma Global Development
- The opinions expressed are my and not necessarily of Astellas or the various associations that I will tell you about in a moment.

My introduction to pro-arrhythmic risk

- I have worked in industry discovering and developing new medicines for >30 years.
- Twenty years ago I worked on an inhibitor of leukotriene biosynthesis from discovery into phase 2 PoC.
- Very low oral bioavailability, so delivered by inhalation.
- As we started the phase 2 PoC in asthma patients a colleague had an idea for a better oral formulation which my group tested in dogs.
- Two of six dogs dropped dead 45 minutes after dosing.

Company & cross-company activities for cardiac safety

- Since 1990s on Drug Metabolism & Clinical Pharmacology groups of PhRMA, now IQ Consortium.
- 2004-5: on Astellas task force for guideline on cardiac safety. Led two subsequent updates.
- 2009 – present: ICH E14 Implementation Working Group. Developed 5 Q&As. Two more in process.
- 2009 – present: Optimizing QT group. Focus on applying concentration-QTc relationships
- December 2011 – present: IQ-CSRC group on use of ECG data from early phase 1 to replace TQT study.

Challenges

- How to extrapolate animal or human in vitro data to the clinic.
- Variability in ECG intervals larger than the drug effect that we want to detect.
- Multiplicity: if you dose placebo and measure QTc 20 times with an adequately powered study and $p<0.05$ you will usually get a false positive.

Approach in industry

- Safety pharmacology: hERG and ECGs in dogs or monkeys. Except for oncology and drugs intended to affect cardiac rhythm, stop positive compounds.
- ECG intervals in early phase 1 SAD and MAD. Except for oncology and drugs intended to affect cardiac rhythm, stop compounds that prolong QTc.
- In phase 2b conduct TQT study and try to avoid false positive results

Example of ECG assessment in a SAD study

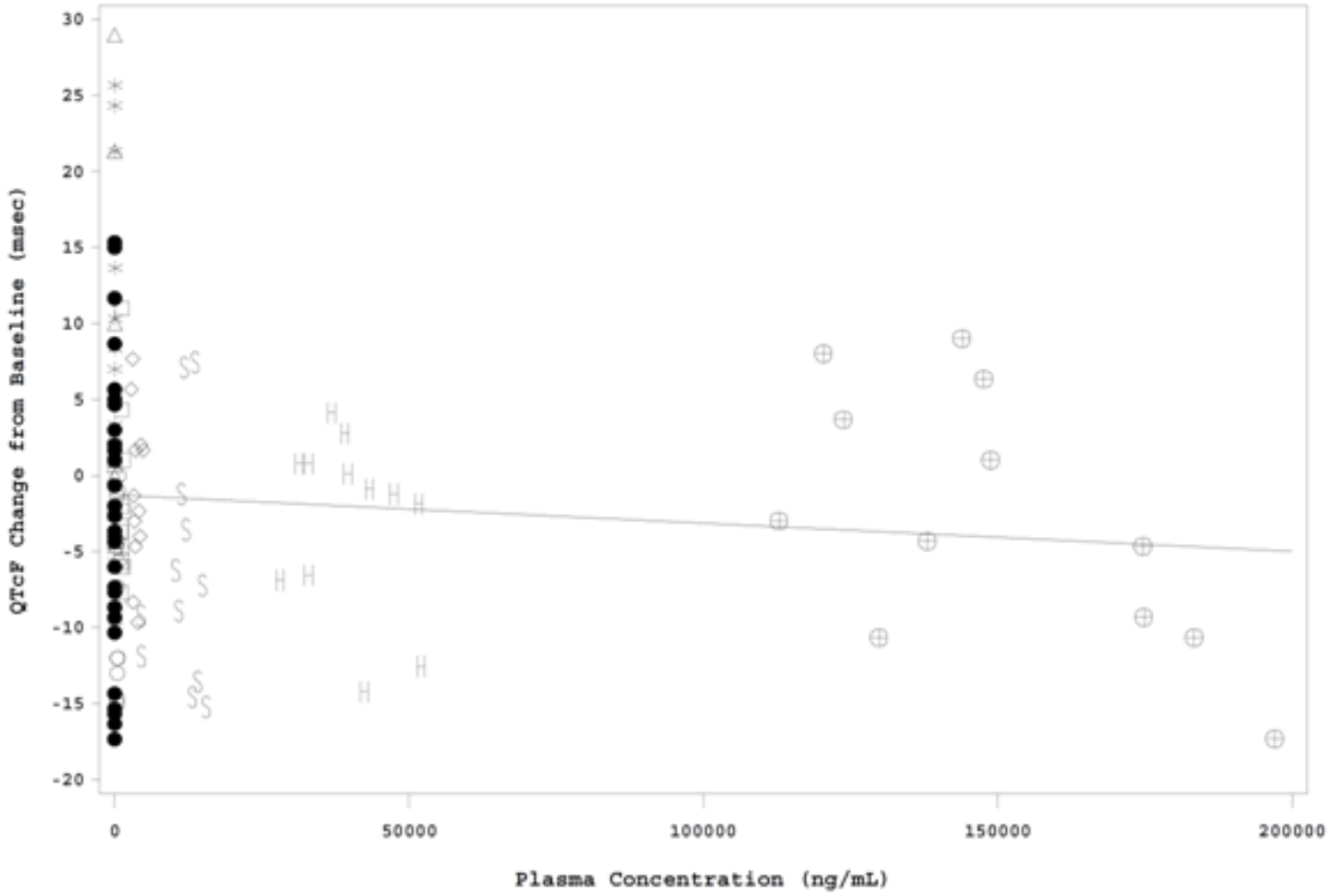
- MAb that targets a protein on the surface of lymphocytes
- 30 min infusion
- ECGs: predose, 3 h, 5 h, 24 h, 1 wk, 2 mo

Cohort	Route	Dose	Active (N)	Placebo (N)
A	iv	0.003 mg/kg	6	3
B	iv	0.01	6	2
C	iv	0.03	6	2
D	iv	0.1	6	2
E	iv	0.3	6	2
F	iv	1.0	6	2
G	iv	3	6	2
H	iv	10	6	2

Categorical & by timepoint analysis

- No QTcF interval exceeded 450 msec
- No changes from baseline greater than 60 msec were observed.
- QTcF interval changes greater than 30 msec but less than 60 msec were observed in one subject who received placebo, one subject who received active 0.03 mg/kg and one subject who received active 1.0 mg/kg.
- In the assessment of ECGs conducted at 3 and 5 hours postdose, no treatment effect for differences from placebo were observed on mean QTc prolongation except for the 2 lowest doses of active. The mean QTc prolongations at 3 and 5 hours postdose after the intravenous infusion of active 0.003 mg/kg were 6.72 msec (90% 2-sided CI: 0.24, 13.19) and 7.16 msec (90% 2-sided CI: 0.69, 13.64), respectively. The mean QTc prolongations at 3 and 5 hours postdose after the intravenous infusion of active 0.01 mg/kg were 11.01 msec (90% 2-sided CI: 4.51, 17.50) and 8.90 msec (90% 2-sided CI: 2.40, 15.40).

Concentration-QTcF



Mechanisms for drug-induced arrhythmogenicity

- direct effects on cardiac ion channels/pumps
- effects on expression of ion channels (such as inhibition of ion channel trafficking),
- indirect effects on arrhythmogenicity such as:
  - changes in autonomic nervous system activity,
  - hormones (decrease in blood testosterone etc.),
  - and electrolytes (decrease in blood K or Ca etc.)

What is the predictive value in adding additional ion channels?

- Translation to the clinical has been seen for hERG, Na+ and to some extent, Ca2+
- Really not the case for IKs, IK1 and slow Na+ current, when it comes to the level of block required to have a clinical effect.
- The hit rate on these channels is so low that one large pharma company has stopped routinely screening for the slow Na+, IK1 and IKs channels, even though the later it is involved in LQT

TQT de-risks phase 3 and post marketing

- Without a TQT study, how will the Sponsor counter the occasional spurious finding of QTc prolongation?
- Artifacts abound in the clinical setting.
- Without a negative TQT, will there be sufficient evidence for the sponsor to stand on, if an occasional QTc prolongation or arrhythmic event occurs?

Closing Questions

- We have a lot of data using the current paradigm. How do we generate robust data to validate the proposed new paradigm?
- Metabolites?
- How will we include the regulators outside the USA? ICH?
- How do get the new methods available in multiple labs?
- In silico models have been around for decades. How do we get them adopted to make routine business decisions on the pro-arrhythmia risk of compounds?