QT Studies for Biologics
Workshop 2

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Cardiac Safety

Reasons for Drug withdrawal

- Cardiotoxicity: 42%
- Hepatotoxicity: 37%
- Drug interactions: 8%
- CNS: 5%
- Other: 8%

Shah RR, 2006
...is here to stay
## Drug Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Cardiotoxicity</th>
<th>Key features</th>
<th>Regulatory guidance</th>
</tr>
</thead>
</table>
| **Repolarization and Conduction Related Cardiotoxicity** | • Assesses risk for drug induced arrhythmia and sudden death  
  • Endpoint Variable – ECG QT/QTc Interval Prolongation; PR and QRS Intervals.  
  • Examples – hERG Blockers - Terfenadine, Cisapride, etc | ICH-E14 guidance                  |
| **Vascular Related Cardiotoxicity**                | • Assesses Risk for Drug Induced Vascular/Thrombosis Events  
  • Endpoint – CV events such as ACS, MI, CHF, Stroke, Death; Biomarkers, Imaging, ECG  
  • Examples – T2DM drugs (e.g., Rosiglitazone)  
  • COX-2 inhibitors (e.g., Vioxx) | FDA & EMA Type 2 Diabetes guidance                  |
| **Tissue Related Cardiotoxicity**                  | • Assesses Propensity of NCE to Cause Direct Tissue Damage  
  • Endpoint – HF, Death; Serum Biomarkers, Imaging and ECG  
  • Examples – Oncology Drugs, e.g., Trastuzumab (Herceptin) | No Guidance (yet)                  |

Mendzelevski B, 2010
Across the Atlantic
Electrocardiographic assessment for therapeutic proteins—scientific discussion

Ignacio Rodriguez, MD, Andrew Erdman, MD, Desmond Padhi, PharmD, Christine E. Garnett, PharmD, Hong Zhao, PhD, Shari L. Targum, MD, Suchitra Balakrishnan, MD, PhD, Colette Strnadova, PhD, Norman Viner, MD, Mary Jane Geiger, MD, PhD, Christopher Newton-Cheh, MD, MPH, Jeffrey Litwin, MD, Michael K. Pugsley, PhD, Philip T. Sager, MD, Mitchell W. Krucoff, MD, and John K. Finkle, MD

Electrocardiographic monitoring is an integral component of the clinical assessment of cardiac safety of all compounds in development. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline recommends a dedicated study to evaluate drug-induced effects on cardiac repolarization (“thorought QT/QTc study”). There has been limited published information on QT interval changes secondary to therapeutic proteins; however, in theory, biologic therapies may affect cardiac electrical activity either directly or indirectly. This article summarizes scientific discussions of members of the Cardiac Safety Research Consortium and includes possible approaches to consider for the clinical evaluation of drug-induced QT prolongation in development programs of therapeutic proteins. (Am Heart J 2010;160:627-34.)
“...The ICH E14 guidance document was written with an emphasis on small molecule drugs and does not specifically address the QT assessment for therapeutic proteins. There is currently no consensus about whether and how to apply the principles of ICH E14 to therapeutic proteins or, more broadly, what level of clinical QT assessment is necessary for such therapies...”
# Functional Classification and MW

<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Molecular Weight</th>
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<tbody>
<tr>
<td><strong>Ia</strong> (replacement)</td>
<td>Insulin</td>
<td>5,808Da</td>
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<tr>
<td></td>
<td>Growth Hormone</td>
<td>22kDa</td>
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<tr>
<td><strong>Ib</strong> (augmentation)</td>
<td>Erythropoietin</td>
<td>34kDa</td>
</tr>
<tr>
<td></td>
<td>Interferon</td>
<td>40-60kDa</td>
</tr>
<tr>
<td><strong>Ic</strong> (novel function)</td>
<td>Botulinum toxin (crude)</td>
<td>190kDa</td>
</tr>
<tr>
<td></td>
<td>Xeomin</td>
<td>150kDa</td>
</tr>
<tr>
<td></td>
<td>Streptokinase</td>
<td>47kDa</td>
</tr>
<tr>
<td></td>
<td>Bivalirudin</td>
<td>2,180Da</td>
</tr>
<tr>
<td><strong>IIa</strong> (interfering)</td>
<td>Monoclonal antibodies</td>
<td>150kDa</td>
</tr>
<tr>
<td><strong>IIb</strong> (delivering)</td>
<td>Gemtuzumab ozogamicin</td>
<td>151-153kDa</td>
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</table>

Adapted from Leader et al. Nat Rev Drug Discovery 2008;7;21-39
Small molecules of a MW<1kDa may inhibit the hERG Channel by
1. entering the cardiac myocyte and
2. binding to amino acid residues Y/F on the inner pore surface of the ion channel

Molecules with a MW 1,000 - 25,000 Da “...rarely have been shown to inhibit the hERG channel function either directly, by binding to extracellular channel domains, or indirectly through other secondary mediators...”


• Insulin prolongs the QTc interval in humans in euglycemic clamp

Fig. 3. The physiological system connecting plasma insulin concentrations with serum potassium levels and the activity of the autonomic nervous system (ANS). (+) and (-) indicate stimulation and inhibition, respectively. See text for explanation.

• Insulin stimulates the muscle sympathetic nerve activity

Fig. 1. Time course of heart rate (top), Q-T interval (middle), and QTc (bottom) during resting conditions and during 100 min of euglycemic hyperinsulinemia in 35 nondiabetic subjects. ■, Means ± SE, bpm, Beats/min.

Food Effect on QTcF (95% CI)

...is it true?

max -8.2 ms

Taubel et al. 2011
Food Effect on QTcB (95% CI)

Taubel et al. 2011
Autonomic Changes

- **QTc prolongation** due to (some examples):
  - Sleep (vagal effect) \(^1\)
  - Brain damage/death (impaired autonomic control) \(^2\)
  - Atropine (removing vagal control) \(^5\)
  - Diabetes (neuropathy impairing vagal control) \(^6\)
  - Gender (differences in autonomic balance?) \(^7\)
  - Food \(^8\)
  - Fasting (hypoglycaemia) \(^9\)

\(^1\) Browne K et al. Am J Cardiol 1982;50:1099–103
\(^2\) Annila et al. Br J of Anaesthesia 71(5):736
\(^3\) References on request
\(^4\) References on request
\(^5\) References on request
\(^6\) References on request
\(^7\) References on request
\(^8\) References on request
\(^9\) Petrov DB, Texas Heart Institute Journal, 30; 1; 86-87; 2003
Preclinical Studies

Vargas et al. Scientific review and recommendations on preclinical cardiovascular safety evaluation of biologics

“...It is more appropriate to assess QTc risk by integrating cardiovascular endpoints into repeat-dose general toxicology studies performed in an appropriate non-rodent species...”

Journal of Pharmacological and Toxicological Methods, Volume 58, Issue 2, September-October 2008, Pages 72-76
Clinical QT Studies?

1. Do the non-clinical studies indicate an effect on ventricular repolarisation?
2. Do early clinical studies indicate a QTc signal?
3. What is the magnitude of the QTc signal?
4. Are there potential drug interactions?
5. Does the drug have unique characteristics?
6. Has your TQT study confirmed the above?
7. What will be your next development step?
Difficulties mastered are opportunities won.

Continuous effort - not strength or intelligence - is the key to unlocking our potential.

Never, never, never give up.

- Winston Churchill
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