Biomarker Surveillance & Combining Modalities: Seeking a "Signature" of Early Cardiotoxicity

Conclusions from Troponin

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Background and Overview

- Drug-induced cardiac toxicity is a recognized challenge in development / use of pharmacoRx
  - Direct myocardial injury, arrhythmias, valvular lesions and ischemic events
  - Secondary effects: BP changes or neurohormonal
- To detect abnormalities early in development and manage cardiotoxicity risk, biomarkers are helpful
- Troponins (T/I) excellent markers of myocardial injury
  - Highly cardio-specific
  - Increasingly sensitive and precise are available

Troponins in Preclinical Development

- Although cTn widely used for preclinical detection of cardiotoxicity, several shortcomings exist
  - Most cTn assays have been developed for human, not animal, studies
  - No direct or obvious way to confirm small cTn elevations associated with micropathology in preclinical studies with cardiac imaging/functional studies in humans with the current technologies
  - Unknown prognostic implications of small cTn elevations in healthy volunteers (HVs) or ambulatory patients not at high risk of ischemic heart disease; therefore, difficult to interpret these types of cTn elevations in early development

Troponins in Clinical Development

- Key considerations
  - Who to include and what is expected cTn variability in those with no active (or background) treatment?
  - What cTn level for dose modification/discontinuation?
  - Which assay should be used?
  - How frequently should samples be analyzed?
  - What is the appropriate follow-up if cTn elevations?
  - How do cTn elevations affect the benefit:risk balance of the compound in development?

Troponins in Clinical Development

- Consideration for cTn monitoring during clinical studies should be entertained when
  - there is a preclinical signal for cardiotoxicity (ischemic or nonischemic) or the potential to exacerbate preexisting disease
    - Clear caveats and unknowns in translating preclinical findings and their implications for drug development
- Single algorithm cannot cover all potential scenarios
  - consensus across stakeholders on assay, monitoring strategy and prospective plans for data interpretation needed early in study design process
- Role in conjunction with other biomarkers requires more study

Next Steps, continued

- Collect data ("cTn Warehouse") to establish
  - further information on epidemiology and prognostic relevance of cTn elevations in various populations (intra- and inter-individual variability in "healthy volunteers"), particularly with newer high or ultra sensitive assays)
  - expected background rates of cTn elevation due to disease state and expected rates of cTn elevation in response to existing treatments for various illnesses
    - randomized clinical trials with a placebo arm provide a unique opportunity to explore these questions.
- In establishing "cTn warehouse," a set of "essential minimum" clinical data about subjects and treatments would need to be established along with the development of a simple data collection tool

Next Steps, continued

- Collect data from sites on all patients enrolled in clinical trials and existing registries/databases, including CMS, both to understand the variability of cTn within and across sites, assays, subjects and by treatment and as exploratory endpoints in clinical trials
  - When MI collected as a primary endpoint, data on timing of cTn relative to clinical event helpful to understand safety profile
  - Whenever possible, correlations of cTn serial levels and serial comparisons of cardiac images would help to better understand significance of modest cTn changes and cardiac toxicity in human subjects

Next Steps, continued

- Engage clinical chemistry community in establishing a “living” database” of assay characteristics and performance metrics
  - Human and animal parameters
  - Consolidate information on sample stability/longevity,
  - Develop parameters for frequency of sampling, particularly with high-sensitivity assays, for early detection of cardiotoxicity
  - Determine whether sex- or age-specific differences in assay interpretation are needed
  - Establish generalizable reference ranges for populations with low probability of cardiovascular disease
- Encourage standardized collection of serum or plasma in clinical trials and registries to store for future analyses