Anticoagulant-Induced Bleeding and Reversal Agents Think Tank Meeting

An Industry Perspective

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Comments are those of the presenters and are not necessarily representative of their employers or all of industry

Traditional Drug Development Approach

- Target Product Profile – strategic document summarizing value proposition
  - Indication (Purpose) – 2 separate situations with reversal agents
    - Rapid reversal of anticoagulant effect to manage active clinically important emergent bleeding (ICH, GIB)
    - Normalization of coagulation parameters and reduction in plasma concentration of TSOAC (target-specific oral anticoagulants) to near or below limit of detection to decrease risk of excessive bleeding ahead of an urgent/elective interventional procedure or surgery
  - Elements driving value
    - Pharmaceutical product description - form/route, dose, administration, frequency; qualities imparted by the PK/PD characteristics
    - Benefit
    - Risk (Safety)
- Cost of Goods
- R & D costs
- Reimbursement
- Business case

Challenges & Considerations

- Relationship between reversal of anticoagulant effect and cessation of bleeding not direct
  - Need restoration of physiologic hemostatic balance, not just normalization of 1 or 2 coagulation parameters, and reduction of plasma concentration of TSOAC
  - Reversal may not prevent the damage (ICH)
  - Preexisting/acquired lesion – bleeding not exclusively due to excess anticoagulant
  - Concomitant antithrombotics (anticoagulant + antiplatelet), new antiplatelet agents, renal and liver disease
  - Attribution of bleeding exclusively to TSOAC is difficult in presence of co-existing reasons
- Medical Need vs. Availability on the Shelf
  - Medical need - number of actual cases that would benefit is unclear
    - Differs for the 2 situations: cessation of emergent bleeding vs. correction of hemostatic parameters toward normal for elective procedure
    - Half-life of TSOACs is short – non-emergent procedures that can wait 24 hr
    - Supportive care effective in phase 3 clinical trials: maintenance of hemodynamics, local hemostasis, compression or appropriate surgical/interventional treatment, blood product support
    - While in the phase 3 clinical trial programs reversal products were rarely used and bleeding managed without antidotes, eventually millions of patients are likely to receive TSOACs
- Across heterogeneous populations
- Specialized laboratory testing

Challenges & Considerations

- Logistics
  - Feasibility
    - Number of cases requiring emergent treatment is far < cases for elective reversal
    - For life-threatening situation, the usual phase 3 trial becomes impractical
      - Infrequent events - requires very large number of sites to capture
      - Recruitment/consent → procedural difficulties when time is of the essence
  - Time to accomplish
    - Collecting sufficient data in realistic time frame
  - Cost issues
    - Number of sites, maintaining study medication supply, etc.
    - For elective situation, likelihood of use goes down as cost of the treatment goes up (COG, market price)
- Reimbursement authorities
  - Unlikely to pay for elective therapy reversal when doctors can dispense tincture of time
- The evidence needed to conclusively prove benefit over current care is not yet clear

Phase 3 End points

- Pharmacodynamic reversal as end point
  - Could PD reversal as confirmation of reversal agent's MOA be enough if safety profile could be established?
    - More quantitative, simpler approach
    - Yet, challenging to distinguish component(s) of bleeding that would be diminished by reversing the PD action of the anticoagulant
  - Recent regulatory advice suggests Phase 2 surrogate data alone insufficient for standard registration (indication of rapid reversal of anticoagulant effect to manage active clinically important emergent bleeding)
    - Outcome data required for approval
    - Consideration to follow Kcentra path (though FFP control)
  - Once agent proven to reverse clinically important bleeding, could be acceptable for indication to decrease risk of bleeding ahead of an urgent/elective interventional procedure or surgery?

Phase 3 End points

- What are acceptable clinical outcomes for achieving clinical hemostasis?
  - Type and severity of bleeding and its location must be considered
  - Kcentra : “hemostatic efficacy” – visible and non-visible bleeding scoring
    - Essentially based on Volume and Time to Cessation
      - Volume of bleeding
        - » Ability to quantify depends on location; element of subjectivity
        - » Hemoglobin
          - Baseline Hb at presentation vs patient’s actual baseline Hb
          - How to account for hemodilution
      - Time Measurement
        - » Cessation: time to stoppage of bleeding (beginning when?)
          - pertinent to emergency bleeding but not elective situation (what about surgically-induced?)
        - » Time to stabilization and time to recovery from bleeding?
  - Other potential clinical outcomes to factor in
    - Interventions to manage the bleeding
    - Resulting morbidity
    - All-cause death (during hospitalization or at 30 days)
    - Subsequent worsening of bleeding
    - Prothrombotic events

Benefit - Risk

- Benefit
  - Clinical efficacy (pharmacodynamic outcomes not sufficiently convincing)
  - Supplementary
    - QOL (e.g., Rankin)
    - Healthcare Resource (e.g., hospitalization)
- Risk (Safety)
  - Procoagulant/Prothrombotic state – "overshoot" in attempt to counterbalance hemostatic system
  - Need for repeated infusion, neutralizing antibodies, infusion reactions
  - Drug – Drug Interactions
  - Off target effects/AE's (separate from those of on-going restoration measures)
  - Potential long term consequences (immunogenicity, accumulation in end organs)
- Caveats
  - ❑ Response of bleeding specific to the reversal agent is difficult to quantify
    - ❖ More than one treatment is given in emergency
  - ❑ Additional risk may be acceptable when attempting to reverse catastrophic bleeding

Well-Designed Clinical Trial

- Clinical development program path
  - Development program needed for reversal of each TSOAC
  - Develop in each indication of anticoagulant approved use? No.
    - Sets a very high bar - requires a clinical trial (at least one) in each indication
  - Instead, focus on bleeding patient population and their baseline characteristics
    - Bleeding not driven by indication for anticoagulant approved use (e.g., VTE treatment, AF)
      - e.g., with warfarin – more dependent on INR level and duration spent there, age, renal function, uncontrolled HTN, Hx prior bleeding, etc.
- Clarification around outcomes requiring reversal
  - Agree on the clinical outcomes for achieving clinical hemostasis
  - Agree on number of events acceptable, given infrequency
  - Agree on acceptable methods of adjudication, noting challenges (blinding, subjectivity)
  - Recognize difficulty in accomplishing the trial in reasonable time to make results pertinent to current practice
- Statistical analysis plan
  - Success = randomized, clear outcome, pre-specified statistical analysis plan, and we power study to detect a difference in end point
  - Here, we are unsure of the end points, our ability to alter the end points, how much impact we will have on the end points, and the variability in those end points

Well-Designed Clinical Trial

- Is there a feasible experimental design for a pivotal trial to collect a sufficient quantity of representative data in a reasonable period of time?
  - Typical phase 3 RCT impractical
  - Alternatives to RCT less compelling
    - Nonrandomized controlled trials
      - Would require confirmation by a randomized study or meta-analysis of similarly designed studies
    - Uncontrolled trials – with no concurrent comparison, they are unreliable
    - Phase 2 POC study (persuasive result) followed by Registry (ACC NCDR) or Real World Evidence trial?
    - Adaptive study size and dosing regimen, guided by DSMB
  - Comparator
    - Randomized
      - **Placebo: Acceptable?** Time window to do so is limited
      - Active comparator: none approved
    - Nonrandomized
      - Historical controls –"no go"?
      - Without randomization, cannot convincingly assess efficacy or even comparative safety
    - Contemporary controls (SOC) cohort, followed by experimental agent cohort
- Follow-up Observation period
- Assessment of reinstitution of anticoagulation after reversal

Summary

- TSOACs provide benefit that in most patients outweighs the risk
  - Reversal agents if easily administered, rapid-acting, & readily available, have potential to further improve balance
  - A certain tension exists between unmet need and desire to have
  - Relationship between reversal of anticoagulant effect and cessation of bleeding not direct
  - Relatively short half-life of current TSOACs
  - 2 Indications: 1) Rapid reversal of active clinically important bleeding, and 2) normalization of coagulation parameters and reduction in plasma concentration in advance of urgent/elective interventional procedure or surgery
- Alternative approaches to the traditional phase 3 RCT are warranted
  - Defining the ideal pivotal trial design, comparator, and outcome is not straightforward
  - Feasibility in question, populations heterogeneous, events infrequent, logistics, time
  - Focus on bleeding patient population as opposed to focus on indication for anticoagulant approved use
  - Registry, post-marketing, "real world evidence" studies could provide supportive clinical outcome data
- Availability of a specialized lab test with very rapid turnaround to confirm MOA of anticoagulant on board and level of anticoagulation could refine choice of reversal agent(s), dose(s), and effect
- Meanwhile, continued emphasis on standardized guidance and continuous healthcare provider education re: the general management of patients with or at risk for serious bleeding
  - What measures to apply first in bleeding patients
  - When is it appropriate to administer a reversal agent
  - Which agents should not be administered in certain settings

BACKUPS

Session III: What are the most viable development strategies for NOAC reversal agents?

- What clinical endpoints would be acceptable (e.g., clinically meaningful, reliable and practical) for Phase 3 or 3b studies of reversal agents for NOACs?
  - How would the benefit: risk relationship be defined?
  - Is it NOAC indication-specific?
  - What data would be needed to support reversal agent use in practice?

Session III: What are the most viable development strategies for NOAC reversal agents?

- <u>What would a well-designed study with a reversal agent look like?</u>
  - What patients would be most appropriate to study?
  - What are the practical limitations for conducting Phase 3/3b with NOAC reversal agents?
  - How should bleeding be attributed to NOACs vs. underlying disease or clinical condition?