Reversing Agents -
The Post-Marketing Big Picture

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Reversing Agents
The Post-Marketing (PM) Big Picture

• What are the important components of safety and efficacy that are incompletely defined at approval?

• What are the tools available to define these in a post-marketing environment?
What are the important components of safety and efficacy that are undefined at approval?

- The design and findings of the clinical trials determine the need for PM data.

- What variables can affect efficacy outcomes?
  - Indication for reversal: major bleeding type (e.g., ICH, GI, trauma), or urgent surgery
  - Indication for anticoagulation: AF, VTE prevention - surgery, 1°, 2°
  - NOAC dose, time from dose, GFR
  - Comorbidity: age, organ function, concomitant disease
  - Concomitant medication: especially hemostatically active meds
  - Laboratory criteria: standard coagulation, agent specific, TEG, other
What are the tools available to define **efficacy** better in a post-marketing environment?

- **Post-marketing commitments - voluntary**
- **Post-marketing requirement for products under Accelerated Approval - required**

**Clinical trials:**

- Confirmation of surrogate end points
  - Analogous to vitamin K antagonist (VKA) reversal trials
- Defining efficacy in specific subpopulations
What are the important components of safety and efficacy that are undefined at approval?

The design and findings of the pivotal clinical trials determine the need for PM data

➢ Safety challenges
  – A single arm trial has an inherent problem isolating adverse drug effects
  – The exposed population is medically complex
  – By definition, observation of rare events is proportional to the size of the trial population
What are the important components of safety and efficacy that are undefined at approval?

- Potential Safety Issues
  - Thrombosis
  - Immunogenicity
  - Hypersensitivity
  - DIC
  - Drug ineffective
  - Unpredicted serious adverse events
What are the tools available to define safety better in a post-marketing environment?

Post-Marketing Requirements under the FDA Amendments Act of 2007

- Clinical trials: with controls, and trials in specific populations*
- Observational epidemiologic studies
- Enhanced pharmacovigilance (PV): targeted, dependent on voluntary reporting, registries
- Electronic Health Record, observational: suitable for agents with high use, identifiable events, and an appropriate comparator
What are the tools available to define safety better in a post-marketing environment?

- **Standard Pharmacovigilance**
  - Voluntary, estimated reporting rates 1-10% of serious events
  - Most effective for rare, serious events
  - No denominator, so no rates
  - Potential for under representation/biased reporting

- **Risk Evaluation and Mitigation Strategy with Elements To Assure Safe Use**
  - natalizumab (Tysabri) and PML
  - PTH (Natpara) and osteosarcoma
Post-marketing data for NOAC reversing agents

Plausible Adverse Events

• VTE and ATE
  – Causation is unlikely to be determined by spontaneous reporting due to disease confounding
  – EHR observational studies: low use, and difficult comparator
  – Risk factors identification: uncertainty regarding proportional reporting

• Allergic and hypersensitivity reactions
  – Reversing agents are proteins
  – Spontaneous reporting may define severity, not incidence
Post-marketing data for NOAC reversing agents

Plausible Adverse Events

- **Immunogenicity**: would require specific monitoring to detect new antibody
- **Therapy ineffective**
  - “Success” rate with VKA reversal is ~ 70%
  - Bleeding is a multifactorial event
- **Disseminated Intravascular Coagulation**
  - Usual diagnostic criteria need investigation in the context of reversing agents’ use
  - Outside of a clinical trial, specialized lab studies are unrealistic for the PM context
Expectations of Post-Marketing Data Should be Realistic
The drug approval balance: rapidly available – thoroughly defined
Post-marketing data for NOAC reversing agents

Wish List for evaluating PM events

- Indication for NOAC
- Time from last NOAC dose and mg dose
- Serum creatinine and calculated GFR
- Evaluations of hemostatic function
- Specific criteria for use of reversing agent
- Standard elements: con meds, pertinent medical Hx
- Logical narrative
Back-up
NOAC PK with GFR > 79 ml/min

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<td>Rivaroxaban</td>
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* No dose adjustment for decreased GFR
Major Bleeding risks in pivotal trials

Apixaban 2.1/ 100 PY
Dabigatran 3.4/ 100 PY
Edoxaban 3.1/ 100 PY
Rivaroxaban 3.6/ 100 PY

Dabigatran trial urgent surgery (US)
248/12,279 (2%) underwent US
44/248 (18%) had a major bleed (MB) with US
44/12279 (0.36%) of total had MB with US
MB incidence US = 5.4 x elective surgery
ETASU for Natpara (PTH)

- Prescribers must become certified in the NATPARA REMS Program to be able to prescribe NATPARA

- Pharmacies must be certified to dispense NATPARA

- NATPARA must be dispensed only to patients informed about the potential risk of osteosarcoma associated with the use of NATPARA
ETASU for natalizumab (Tysabri)

- Education
- Requirement to complete a questionnaire at drug discontinuation, and at 6 months after discontinuation
- Statement that cases of PML, hospitalizations due to opportunistic infection, or deaths be reported to Sponsor ASAP