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

	elimination t ½	time to Cmax
Apixaban*	12	3-4
Dabigatran	12-17	1
Edoxaban	10-14	1-2
Rivaroxaban	5-9	2-4

* 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**