Pipeline Agents for NOAC Reversal

Sandy Bartlett, PhD, PharmD, BCPS
Associate Professor | Department of Pharmacy Practice
Conflict of Interest

- I have no actual or potential conflict of interest in relation to this program to disclose.
Learning Objectives

- Identify three molecular entities that are currently in development for reversal of NOACs
- Compare the drug design strategy for each of these new pipeline reversal agents that are currently in clinical trials
- Evaluate how these potential new agents may be incorporated into a treatment strategy for significant bleeding related to NOAC use based on patient specific information
New Oral Anticoagulants (NOACs)
Dabigatran (Boehringer Ingelheim)

- FDA approvals
  - NVAF
    - October 2010
  - DVT/PE Treatment
    - April 2014

Rivaroxaban (Janssen)

- FDA approvals
  - NVAF
    - November 2011
  - DVT/PE
    - November 2012
  - Knee/Hip VTE
    - July 2011

Apixaban (Bristol-Myers Squibb)

- FDA approvals
  - NVAF
    - December 2012
  - DVT/PE Treatment
    - August 2014
  - Knee/Hip VTE Prevention
    - March 2014

Edoxaban (Daiichi Sankyo)

- FDA approvals
  - NVAF
    - January 2015
  - DVT/PE Treatment
    - January 2015

NOAC Targets

Patient taking NOACs may still experience

- Major bleeding complications
  - Similar or lower bleeding rates than with warfarin
- Trauma injuries
- Require urgent / emergent surgery

Learning Objectives

- Identify three molecular entities that are currently in development for reversal of new oral anticoagulant (NOAC) agent(s)

- Compare the drug design strategy for each of these new pipeline reversal agents that are currently in clinical trials

- Evaluate how these potential new agents may be incorporated into a treatment strategy for significant bleeding related to NOAC use based on patient specific information
Pipeline Reversal Agents

- Idarucizumab (Boehringer Ingelheim)
- Andexanet alfa (Portola Pharmaceuticals)
- Aripazine (Perosphere)
Learning Objectives

- Identify three molecular entities that are currently in development for reversal of new oral anticoagulant (NOAC) agent(s)

- Compare the drug design strategy for each of these new pipeline reversal agents that are currently in clinical trials

- Evaluate how these potential new agents may be incorporated into a treatment strategy for significant bleeding related to NOAC use based on patient specific information
Pipeline Agents for NOAC Reversal

IDARUCIZUMAB
Idarucizumab

- Humanized mAb fragment against dabigatran

- Target
  - Dabigatran

http://www.rcsb.org/pdb/explore/explore.do?structureId=4YGV

Tight Binding Affinity for Dabigatran

- Binding affinity is 350-fold higher for idarucizumab over thrombin

<table>
<thead>
<tr>
<th>Ligand – Target Binding</th>
<th>K_D (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran - Thrombin</td>
<td>0.7</td>
</tr>
<tr>
<td>Dabigatran - Idarucizumab</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Dabigatran Binding to Idarucizumab

RE-VERSE AD™ Interim Results

- **REVERSE** Sal **E**ffects of Idarucizumab in Patients on **Active** Dabigatran

- Phase 3 multicenter, prospective cohort study
  - Group A: Uncontrollable or life-threatening bleeding (n=51)
  - Group B: Urgent surgery or intervention (n=39)

- Intervention
  - Patient received idarucizumab 5 g IV
    - Two 50 mL bolus infusions ≤ 15 minutes apart

RE-VERSE AD Interim Results

- Primary end point
  - Maximal reversal of dabigatran based on laboratory assessment within 4 h after idarucizumab administration
    - Dilute thrombin time or ecarin clotting time

- Results
  - Median maximum reversal = 100%
    - 68/90 patients (75%) had an elevated dilute thrombin time at baseline
    - 81/90 patients (90%) had an elevated ecarin clotting time at baseline

Successful Reversal in Bleeding Patients

Successful Reversal for Urgent Procedures

B Concentration of Unbound Dabigatran in Group B

Unbound Dabigatran (ng/ml)

Time of Blood Sample

Pipeline Agents for NOAC Reversal

ANDEXANET ALFA
Andexanet alfa

- Modified recombinant Factor X protein expressed in CHO cells

- Targets
  - Factor Xa inhibitors
    - Rivaroxaban, Apixaban, Edoxaban
  - LMWH & Fondaparinux

Andexanet Protein Design

- Modifications to Factor Xa

- Removal of the activation peptide and replace with RKR to form the linker that connects the light chain to the heavy chain

Andexanet Protein Design

- Modifications to Factor Xa to prevent procoagulant activity

- Mutation of Ser → Ala in active site

Andexanet Protein Design

- Modifications to Factor Xa to prevent anticoagulant activity

- Removal of $\gamma$-carboxyglutamic acid membrane binding domain

Decoy Mechanism for NOACs

- Decoy binds NOACs and reverses Factor Xa inhibition and restores ability to generate thrombin for hemostasis

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Andexanet $K_D$ (nM)</th>
<th>Factor Xa $K_D$ (nM)</th>
<th>Affinity $\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>0.58</td>
<td>0.100</td>
<td>5.8-fold ↓</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.53</td>
<td>0.400</td>
<td>3.8-fold ↓</td>
</tr>
</tbody>
</table>

Andexanet Reverses Rivaroxaban in Rabbit Liver Laceration Model

- 75 mg andexanet IV reduces blood loss by > 85% in rivaroxaban treated rabbits (1 mg/kg)

Andexanet Infusion Achieved Sustained Reversal of Apixaban Anticoagulation

- Phase 2 placebo controlled trial in healthy volunteers
  - 5 mg PO Apixaban BID x 5 days

Pipeline Agents for NOAC Reversal

ARIPAZINE (PER977)
Aripazine

- Small molecule inhibitor

- Targets
  - UFH
  - LMWH & Fondaparinux
  - Factor Xa inhibitors
    - Rivaroxaban, Apixaban, Edoxaban
  - Thrombin inhibitors
    - Dabigatran

Aripazine Forms H-bonds with NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>H-Bond Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixiban</td>
<td>Green</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Red</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Green</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Yellow</td>
</tr>
</tbody>
</table>

Aripazine Reverses Rivaroxaban in Rat Tail Transection Model

- 12.5 mg IV aripazine reduces blood loss to control in treated rats
  - rivaroxaban, apixaban or dabigatran

Apirazone to Reverse Edoxaban

- Phase 2, prospective, double-blind, placebo-controlled trial
  - Healthy persons (n=80)

- Intervention
  - Subjects received escalating doses of aripazine (5 – 300 mg) IV
    - Alone
    - After 60 mg PO edoxaban

Apirazine to Reverse Edoxaban

- Primary end point
  - Whole blood clotting time (WBCT) used to determine
    - Anticoagulant effect of edoxaban
    - Reversal of edoxaban by aripazine

Successful Reversal of Edoxaban

- WBCT decreased to within 10% above baseline in \( \leq 10 \) min
- Remained at \( \pm 10\% \) of baseline for 24h after 1 dose of antidote

### Comparison Summary For Pipeline Agents

<table>
<thead>
<tr>
<th>Pipeline Entity</th>
<th>Design Strategy</th>
<th>Reversal Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Humanized mAb against dabigatran; designed similar in structure to dabigatran-binding pockets of thrombin</td>
<td>dabigatran</td>
</tr>
<tr>
<td>Andexanet alfa</td>
<td>Modified Factor Xa protein to be a decoy target for NOACs</td>
<td>LMWH &amp; fondaparinux Factor Xa inhibitors</td>
</tr>
<tr>
<td>Aripazine</td>
<td>Small molecule designed for non-covalent interaction with anticoagulant; has potential to be “universal” antidote</td>
<td>UFH LMWH &amp; fondaparinux Factor Xa inhibitors Thrombin Inhibitor</td>
</tr>
</tbody>
</table>

UFH = unfractionated heparin  
LMWH = low molecular weight heparin  
Factor Xa inhibitors = apixaban, edoxaban & rivaroxaban  
Thrombin inhibitor = dabigatran
Learning Objectives

- Identify three molecular entities that are currently in development for reversal of new oral anticoagulant (NOAC) agent(s)

- Compare the drug design strategy for each of these new pipeline reversal agents that are currently in clinical trials

- Evaluate how these potential new agents may be incorporated into a treatment strategy for significant bleeding related to NOAC use based on patient specific information
Pipeline Agents for NOAC Reversal

PATIENT CASE
**Patient Case**

- **CC:** BB is a 39 y/o female who presents to the ED at a Critical Access Hospital with fatigue, dyspnea, lightheadedness, abdominal pain, low back pain and vaginal bleeding

- **HPI:** Two week history of vaginal bleeding

- **PMH:** Recent bilateral pulmonary emboli currently being treated with a NOAC. Changed from warfarin to NOAC ~ 6 weeks ago due to distance to anticoagulation clinic. NKDA.

Patient Case

- **Physical Exam:**
  - VS: BP 122/70, HR 79 bpm, RR 18 bpm with O$_2$ sat of 99% on RA; temp 36°C
  - Pelvic exam: fresh blood with clots in vaginal vault and bleeding from closed cervical os

- **Medication Reconciliation**
  - Patient doesn’t recall name of medication but thinks it is something that ends with “ban”. Last dose 2 hrs PTA.
  - Patient’s pharmacy is currently closed, no access to clinic records and no family available.

Patient Case

- Pertinent Labs:

<table>
<thead>
<tr>
<th>Result</th>
<th>Hospital Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Patient Case

1. Based on patient review do you recommend reversal of anticoagulation?
   - Yes
   - No

2. Which agent(s) would be most appropriate?
   (Assume all pipeline agents are FDA approved)
   - A. Idarucizumab
   - B. Andexanet alfa
   - C. Aripazine

Pipeline Agents for NOAC Reversal

POST-LECTURE QUESTIONS
1. Which of the following is a potential reversal agent for dabigatran?

A. trastuzumab  
B. idarucizumab  
C. andexanet alfa  
D. aripiprazole
2. Which of the following molecular entities is designed as a factor Xa decoy?

A. prothrombin complex concentrate (PCC)
B. aripazine
C. andexanet alfa
D. idarucizumab
Post-Lecture Test Questions

3. Which of the following pipeline reversal agents could potentially be used as a “universal” reversal agent for low molecular weight heparins, factor Xa inhibitors and direct thrombin inhibitors?

A. idarucizumab
B. andexanet alfa
C. aripazine
D. protamine