Andexanet vs. PCC for fXa Inhibitor associated Life-Threatening Bleeding

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- Seton Dell Medical School Stroke Institute
Conflict of Interest Statement

Consulting; Significant; Population Health Research Institute at McMaster University.

Honoraria; Significant; CSL Behring.

Consultant/Advisory Board; Modest; Octapharma, Portola
Timeline

1960s-2000s – Warfarin era, only 50% of a fib patients who should be anticoagulated actually are (=200,000 unnecessary strokes per year)
2010 – First DOAC approved
2012 – Trauma Centers’, others’ and patients’ outcry about lack of reversibility, slowing uptake of new and better drugs
2013 – Kcentra Approved for warfarin reversal
2014 -- ANNEXA4 and REVERSE AD cohort studies launched
2015 – FDA approves idarucizumab
2017 – Majeed PCC study published
2018 – FDA approves andexanet alfa, Schulman PCC study published
2019 – ANNEXA-I study launched
Andexanet alfa: Recombinant Modified Human Factor Xa

- Specifically designed to reverse anticoagulant effects of fXa inhibitors
- Acts as a fXa decoy to bind molecules that target and inhibit fXa

*Nature Medicine*, Volume 19, April 2013

- GLA domain removed to prevent anticoagulant effect
- N terminal residues retained to reduce immunogenicity
- S419A: High affinity
- Activity eliminated to prevent thrombin generation

*Nature Medicine*, Volume 19, April 2013
ANNEXA-4 Study Design

**Efficacy Measurements**
- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

**Safety Measurements**
- Thrombotic events
- Antibodies to fX, fXa, andexanet
- 30-day mortality

* apixaban, rivaroxaban, enoxaparin, or edoxaban

**Patient Screening**
- Patient with acute major bleed, meeting inclusion criteria
- If last dose of fXa inhibitor * was within 18 hours

**Andexanet Treatment**
- IV Bolus
- 2-hour IV Infusion
- After end of infusion

**Assessments**
- 1 hr
- 4 hr
- 8 hr
- 12 hr

**Bleeding and Laboratory Assessment**
- Safety follow-up visit

**Day 1**
- Day 3
- Day 30
ANNEXA-4: Design and Analysis Plan

- **Criteria for Major Acute Bleeding**
  - Life-threatening bleeding with hemodynamic compromise
  - Bleeding with hemoglobin drop of >2 gm/dl, or falling below 8 gm/dl
  - Critical organ bleeding, such as intracranial, intra-spinal, etc.

- **Analysis Populations**
  - **Safety** population includes all patients receiving andexanet
  - **Efficacy** population excludes patients with baseline anti-fXa activity <75 ng/ml (0.25IU/ml for enoxaparin) and patients deemed not to meet acute major bleeding criteria by central academic adjudication committee

- **Full Analysis**
  - Includes 352 patients enrolled up to June 1, 2018
Assessment of Clinical Hemostatic Efficacy

- All cases assessed by independent committee
- Specific efficacy criteria for each type of bleed
- Independent Core Lab interpreted brain CT and MRI
- Cases rated as excellent vs. good vs. poor/none
  - For ICH, hematoma volume increase of 0-20% = excellent, 20-35% = good, > 35% = poor/none
  - Based on method developed for assessment of PCC in warfarin reversal*

## Site of Initial Bleeding

<table>
<thead>
<tr>
<th>Safety Versus Efficacy Population</th>
<th>352</th>
<th>254</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracranial Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-traumatic</td>
<td>128</td>
<td>99</td>
</tr>
<tr>
<td>Glasgow Coma Scale, mean</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>NIHSS, mean</td>
<td>5.7</td>
<td>5.2</td>
</tr>
<tr>
<td>mRS, mean</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Trauma related</td>
<td>99</td>
<td>72</td>
</tr>
<tr>
<td>Intracerebral site</td>
<td>137</td>
<td>104</td>
</tr>
<tr>
<td>Hematoma Volume &lt;10cc</td>
<td>84</td>
<td>66</td>
</tr>
<tr>
<td>Hematoma Volume 11-60 cc</td>
<td>53</td>
<td>38</td>
</tr>
<tr>
<td>Sub-dural site</td>
<td>75</td>
<td>58</td>
</tr>
<tr>
<td>Subarachnoid site</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>Time from baseline scan to drug admin, hours (SD)</td>
<td>2.4 (1.6)</td>
<td>2.4 (1.6)</td>
</tr>
<tr>
<td><strong>Gastrointestinal Bleeding</strong></td>
<td>90 (26%)</td>
<td>62 (24%)</td>
</tr>
<tr>
<td>Upper</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Lower</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Unknown</td>
<td>42</td>
<td>27</td>
</tr>
<tr>
<td><strong>Other Bleeding site</strong></td>
<td>35 (10%)</td>
<td>21 (8%)</td>
</tr>
</tbody>
</table>
Main Results: Effective Hemostasis at 12 Hours Post Andexanet

<table>
<thead>
<tr>
<th>Number of Major Bleeds Adjudicated</th>
<th>Number of Patients who Achieved Excellent or Good Hemostasis</th>
<th>Percent of Patients who Achieved Excellent or Good Hemostasis</th>
<th>Binomial Exact 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>249</td>
<td>204*</td>
<td>82%</td>
<td>77% – 87%</td>
</tr>
</tbody>
</table>

* Of 204 patients, 171 (84%) were “excellent” and 33 (16%) were “good”
Anti-fXa Activity in Efficacy Population (N=254)

Example here is apixaban

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Bolus</th>
<th>End of Infusion</th>
<th>4 Hours</th>
<th>8 Hours</th>
<th>12 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>149.7</td>
<td>11.1</td>
<td>11.5</td>
<td>97.2</td>
<td>104.6</td>
<td>91.3</td>
</tr>
<tr>
<td>Percent Change</td>
<td>-92%</td>
<td>-92%</td>
<td>-32%</td>
<td>-34%</td>
<td>-34%</td>
<td>-38%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-93 to -91)</td>
<td>(-93 to -91)</td>
<td>(-38 to -29)</td>
<td>(-36 to -27)</td>
<td>(-41 to -34)</td>
<td></td>
</tr>
</tbody>
</table>
ICH Hematoma Expansion Between 1 and 12 hours

- 71 efficacy evaluable patients had non-traumatic, single-compartment, intraparenchymal hemorrhages
- Of these, 56 had volume expansion ≤ 35% from baseline at 1 hour
- Of these, **55 of 56 (98%)** remained ≤ 35% from baseline at 12 hours *

```
Non-traumatic, single-compartment, efficacy evaluable IPH  N = 71

1 Hour Scan (vs. baseline)
- Volume expansion ≤ 35%  N = 56
- Volume expansion > 35%  N = 15

12 Hour Scan (vs. baseline)
- Volume expansion ≤ 35%  N = 55
- Volume expansion > 35%  N = 1
```
Biomarker-Efficacy Correlation

- Whole treated population – no significant relationship between hemostatic efficacy and reduction in anti-factor Xa activity

- ICH patients – anti-factor Xa activity reduction magnitude was a predictor of hemostatic efficacy

**Graphs:**
- All Patients on Oral FXa Inhibitor
  - Sensitivity vs. 1-specificity
  - AUC (95% CI): 0.53 (0.44 - 0.62)
- ICH Patients on Oral FXa Inhibitor
  - Sensitivity vs. 1-specificity
  - AUC (95% CI): 0.64 (0.53 - 0.74)
Safety – Thrombotic Events

<table>
<thead>
<tr>
<th>Patients in Safety Analysis (N=352)</th>
<th>Total</th>
<th>&lt;6 days after bolus</th>
<th>6-14 days after bolus</th>
<th>15-30 days after bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one thrombotic event within 30 days</td>
<td>34 (9.7%)</td>
<td>11</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ischemic Stroke (or uncertain etiology)</td>
<td>14</td>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>13</td>
<td>1</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary Embolism</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>
Safety – Restarting Anticoagulation

**Thrombotic Events**

<table>
<thead>
<tr>
<th>Patients in Safety Analysis (n=352)</th>
<th>Total</th>
<th>&lt;6 days after bolus</th>
<th>6-14 days after bolus</th>
<th>15-30 days after bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restart of any anticoagulation (includes prophylactic dose heparins)</td>
<td>220 (62%)</td>
<td>145</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>Restart of oral anticoagulation</td>
<td>100 (28%)</td>
<td>31</td>
<td>37</td>
<td>32</td>
</tr>
</tbody>
</table>

**Before** oral anticoagulation restart or never restarted: 34 (9.7%)

**After** oral anticoagulation restart: 0
## Safety – Mortality

<table>
<thead>
<tr>
<th>Patients in Safety Analysis (N=352)</th>
<th>Total</th>
<th>&lt;6 days after bolus</th>
<th>6-14 days after bolus</th>
<th>15-30 days after bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths within 30 days</td>
<td>49 (13.9%)</td>
<td>8</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>35</td>
<td>7</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Non-Cardiovascular</td>
<td>12</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Uncertain Cause</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Mortality Rate by Bleed Type: ICH (15.0%); GI (11.1%)
# Off-Label PCC use in DOAC bleeding


<table>
<thead>
<tr>
<th>Study (Ref.) Characteristic or outcome</th>
<th>Sarode et al(^{16}) (N = 104)</th>
<th>Sarode et al(^{16}) (N = 98)</th>
<th>ANNEXA-4(^{8}) (N = 67)</th>
<th>Majeed et al(^{14}) (N = 84)</th>
<th>This study (N = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant</td>
<td>Warfarin</td>
<td>Warfarin</td>
<td>Xa inhibitors</td>
<td>Xa inhibitors</td>
<td>Xa inhibitors</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Plasma</td>
<td>PCC</td>
<td>Andexanet alfa</td>
<td>PCC</td>
<td>PCC</td>
</tr>
<tr>
<td>Exclusion for poor prognosis</td>
<td>Expected survival &lt; 3 d</td>
<td>Expected survival &lt; 3 d</td>
<td>Expected survival &lt; 1 mo</td>
<td>DNR order given</td>
<td>DNR order given</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>69.8 (13.9)</td>
<td>69.8 (12.8)</td>
<td>77.1 (10.0)</td>
<td>75 (10.9)</td>
<td>76.9 (10.4)</td>
</tr>
<tr>
<td>Male sex</td>
<td>51 (49)</td>
<td>50 (51)</td>
<td>35 (52)</td>
<td>48 (57)</td>
<td>42 (67)</td>
</tr>
<tr>
<td>ICH</td>
<td>12 (12)</td>
<td>12 (12)</td>
<td>28 (42)</td>
<td>59 (70)</td>
<td>36 (55)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>64 (62)</td>
<td>63 (64)</td>
<td>33 (49)</td>
<td>13 (16)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>Time last dose Xa inhibitor to PCC, median (IQR)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>(Mean ± SD)</td>
<td>12.5 (9–16)</td>
<td>16.9 (12–21)</td>
</tr>
</tbody>
</table>

**Effectiveness assessment according to Sarode et al\(^{16}\) for CNS bleeds**

| Excellent or Good\(^{2}\) | 7 (58) | 5 (42) | 16 (80) | Not done | 25 (76)\(^{1}\) |

**Effectiveness assessment according to ISTH criteria\(^{18}\) for CNS bleeds**

| Effective\(^{3}\) | Not done | Not done | Not done | 43 (73) | 25 (69) |

**Safety outcomes during 30 d**

| Thromboembolism | 7 (6) | 8 (8) | 12 (18) | 3 (4) | 5 (8) |
| Death           | 5 (5) | 6 (6) | 10 (15) | 27 (32) | 9 (14) |
Differences Between ANNEXA4 and PCC Studies

- FDA Oversight
- Sample Size
- Independent adjudication for eligibility/efficacy/TE
- Serial CT scans
- Exclusion from efficacy analysis for anti-Xa <75 ng/ml
- PCC mechanism not understood
- Stoichiometry off by as much as 2 orders of magnitude

**ANNEXA-I enrolled 30 patients of 450**
ANNEXA-I Study Design

• Randomized Clinical Trial of AndexXA® in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor (Last dose < 15 hours and symptom onset < 12 hours)

• Primary objective is to evaluate the rate of hemostatic efficacy of andexanet compared to usual care

440 patients receiving a factor Xa inhibitor who are experiencing an acute intracranial bleed

1:1 Rand

Andexanet* (IV Bolus + Infusion)

Usual Care**

30 Day Follow-up

Primary Efficacy Endpoint: Proportion of patients achieving effective hemostasis.

SafetyEndpoints: Occurrence of thrombotic events. All-cause mortality.

*Andexanet

Patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received and the amount and timing of the most recent dose.

**Usual Care

Consists of any treatment(s) (including no treatment) other than andexanet that the Investigator and/or other treating physicians consider to be appropriate.
Main Points –
“Four 3rd graders do not a 12th grader make”

- PCC mechanism not understood
- Stoichiometry does not make sense
- PCC clinical data lacks rigor of FDA regulated trial, e.g. missing follow up CT scans, no anti-Xa levels
- Most antidotes, like andexanet, do not have randomized controlled evidence in sick patients (Just a well understood mechanism and a little safety data)
  - Idarucizumab -- dabigatran
  - Crofab – crotaline envenomation
  - Fomepizole – toxic alcohols
  - Hydroxycobalamin – cyanide
- Andexanet’s mechanism is well understood. It has been studied in multiple small and large animal models, 145 healthy normal and older adults in a placebo controlled RCT, 352 patients with acute major bleeding and ANNEXA-I is ongoing
Questions?