General Heme

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DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant – Amgen, Alexion
What I am Talking About

- ITP
- Sickle cell
- Reversal of Anticoagulation
TPO- Agonist

• Extension/ Safety studies
Eltrombopag

• Extend Study
  – Extension trial

- N = 299
  - Platelet count
    - \( \leq 15,000 \text{ cells/mm}^3 \): 43%
    - 15,001-29,999 cells/mm\(^3\): 27%
    - 30,000-50,000 cells/mm\(^3\): 17%
    - > 50,000 cells/mm\(^3\): 13%
  - Splenectomy: 38%
  - Previous receipt of \( \geq 3 \) ITP therapies: 53%
  - Concomitant use of ITP medication: 33%
Response

- Response ≥ 50,000 : 87%
- Subgroups
  - Splenectomy vs no : 84% vs 89%
  - Use vs no use of previous ITP therapies: 88% vs 87%
  - Baseline platelet count < 30 vs 30,000-50,000 vs > 50,000 cells/mm³: 83% vs 98% vs 95%
Complications

• Thrombosis: 5%
  – Incidence rate: 3.17 per 100
  – Events not correlated with platelet counts

• Liver: 10%
  – All events reversible, most while patient remained on therapy
## Thrombosis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 100 \times 10^9 / L$ vs $&lt; 100 \times 10^9 / L$</td>
<td>0.464 (0.18-1.18)</td>
<td>0.108</td>
</tr>
<tr>
<td>$\geq 150 \times 10^9 / L$ vs $&lt; 150 \times 10^9 / L$</td>
<td>0.432 (0.17-1.10)</td>
<td>0.078</td>
</tr>
<tr>
<td>$\geq 200 \times 10^9 / L$ vs $&lt; 200 \times 10^9 / L$</td>
<td>0.526 (0.20-1.36)</td>
<td>0.185</td>
</tr>
</tbody>
</table>
Reticulin

• No clinically relevant increase in reticulin fiber deposition
  – > 150 patients treated with eltrombopag for > 1 year
  – Also prospective data showing no increase in reticulin
Romiplostim

• Follow-up to 288 weeks
• No new complications seen
• Study patient could use drug at home
  – Still not allowed by FDA
Growth Factors

- Both effective
- Both with low rates of complications
  - Thrombosis rates compatible with controls
- No novel complications
- Reticulin formation less of an issue
Eltrombopag vs Romiplostim

• Eltrombopag
  – Oral
  – Liver and food considerations
  – Limited dose flexibility

• Romiplostim
  – Sub-q weekly
  – Someday home use

• Use dictated by patient preference
Novel Mechanism

- In both long term studies about 5%/yr went into remission
- Higher than would be predicted by natural history of ITP?
Treg

- Impaired Treg function implicated in ITP and other autoimmune diseases
- Tregs increase after rituximab and dexamethasone
Implications

- Drug or increased platelets?
  - Increased TGF-B
- Will long term TPO-A “cure” patients
- Should we be adding other drugs?
- Is this real?
Eltrombopag for MYH9 mutations

- MHY9 mutations associated with thrombocytopenia
  - May-Hegglin
- Phase II trial
  - 12 patients
  - Starting dose 50mg
Eltrombopag for MYH9 mutations

• Results
  – 67% counts > 100,000
  – 25% with doubling counts
  – 1/12 no response

• May be a treatment option for symptomatic patients
TPO-Agonists Wider Use

- Congenital thrombocytopenia
- Aplasia
  - anecdotes
- Chemotherapy
- MDS
Dex vs Pred in ITP

• Although increasingly used, only single arm study data on pulse dex in ITP
• RCT – plts < 30,000
• Dex: 40mg/day x 4
• Pred: 1mg/kg x 4 weeks
Stratified by age
(<40 or ≥40 yrs)

Newly diagnosed ITP patients >15 yrs of age with platelets ≤ 30 x 10⁹/L
(N = 151)

High-dose Dexamethasone
40 mg/day on Days 1-4*
(n = 76)

Assess response at 6 mos

Prednisolone
1 mg/kg/day for 4 wks, then tapered (n = 75)

*Second 4-day course given if platelet count falls ≤ 30 x 10⁹/L within 6 mos in patients who had a platelet count > 30 x 10⁹/L at Day 14.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexamethasone (n = 76 ITT; n = 64 PP)</th>
<th>Prednisolone (n = 75 ITT; n = 70 PP)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained response at 6 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>25</td>
<td>36</td>
<td>.160</td>
</tr>
<tr>
<td>PP</td>
<td>30</td>
<td>39</td>
<td>.363</td>
</tr>
<tr>
<td>Complete response at 6 mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>11</td>
<td>23</td>
<td>.051</td>
</tr>
<tr>
<td>PP</td>
<td>13</td>
<td>24</td>
<td>.119</td>
</tr>
<tr>
<td>Initial response rate at Day 28</td>
<td>47</td>
<td>73</td>
<td>.002</td>
</tr>
</tbody>
</table>
Conclusion

- Standard prednisone better than one dose pulse dex
  - 11% in CR with one dose of dex
- Lower response rates for dex than in single arm studies
Weaning Prednisone

• Comparison of length of prednisone therapy
  – < 8 weeks
  – 8-16 weeks
  – > 16 weeks

• No difference in response

• Higher rate of complications in long term treatment arms
Rituximab for ITP

- Review of published studies
  - Initial response rate 57%
  - 38% one year response rate
  - 5 year response rate
  - Adults – 21%
  - Children - 30%
- Rituximab curative but in only 20% of patients
Rituximab

• Maintenance
  – Small study of every 6 month in ITP and Evan’s patients with one relapse
  – Less relapses
  – Need more data!
Dexamethasone ± Rituximab for New-Onset ITP

Adults, platelet count ≤ 20 x 10^9/L

1° endpoint: platelets ≥ 50 x 10^9/L with no additional therapy at 6 months

N = 101

n = 52

Dex
40 mg/day
Days 1-4

(PP)

Dex +
Ritux 375 mg/m²
Days 7, 14, 21, 28

n = 49

(ITT)

Day 30 - 6 mos

Platelets > 20 x 10^9/L

FU at 6 mos

Platelets ≤ 20 x 10^9/L

N = 101

n = 52

n = 49
<table>
<thead>
<tr>
<th>Patients</th>
<th>SR</th>
<th>SR 100</th>
<th>SR 150</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Platelets 50 × 10^9/L or greater</td>
<td>Platelets 100 × 10^9/L or greater</td>
<td>Platelets 150 × 10^9/L or greater</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>plus rituximab</td>
<td>plus rituximab</td>
<td>plus rituximab</td>
</tr>
<tr>
<td></td>
<td>( P )</td>
<td>( P )</td>
<td>( P )</td>
</tr>
<tr>
<td>Evaluable</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>19 (36)</td>
<td>17 (33)</td>
<td>13 (25)</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>49</td>
<td>49</td>
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<tr>
<td></td>
<td>31 (63)</td>
<td>26 (53)</td>
<td>21 (43)</td>
</tr>
<tr>
<td></td>
<td>.004</td>
<td>.019</td>
<td>.029</td>
</tr>
</tbody>
</table>
Table 3. Effects of treatment with dexamethasone plus rituximab salvage therapy in 27 patients previously allocated to dexamethasone monotherapy who failed to achieve sustained response (overall SR: platelet count ≥ 50 × 10^9/L; SR 100: platelet count ≥ 100 × 10^9/L; SR 150: platelet count ≥ 150 × 10^9/L)

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>SR 100</th>
<th>SR 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets 50 × 10^9/L or greater</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>15 (56%)</td>
<td>12 (44%)</td>
<td>10 (37%)</td>
</tr>
</tbody>
</table>

Table 2. Effects of treatment with dexamethasone or dexamethasone plus rituximab on the rates of sustained response (overall SR: platelet count ≥ 50 × 10^9/L; SR 100: platelet count ≥ 100 × 10^9/L; SR 150: platelet count ≥ 150 × 10^9/L)

<table>
<thead>
<tr>
<th></th>
<th>SR</th>
<th>SR 100</th>
<th>SR 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets 50 × 10^9/L or greater</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone plus rituximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluateable Responders, n (%)</td>
<td>52</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>49</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>n (%)</td>
<td>19 (36)</td>
<td>17 (33)</td>
<td>13 (25)</td>
</tr>
</tbody>
</table>
Bottom Line

• Dexamethasone effective in 1/3 of patients
• Dex + Rit increases response
• No difference with waiting on rituximab??
Dexamethasone

• Increasing data that early control may be of benefit
  – Less toxicity
  – Less change for “epitope spread”

• Increasing positive data for multiple courses of dexamethasone
GIMEMA: Dexamethasone as Initial Treatment for ITP

• 2 prospective pilot studies (single center and multicenter)
• New-onset ITP, platelets: <20-30 x 10⁹/L
• Pulses of high-dose dexamethasone
  – Cycle: 40 mg daily PO or IV for 4 days
• Response evaluation
  – CR: platelets >150 x 10⁹/L
  – PR: platelets >50 x 10⁹/L
  – MR: platelets >20-30 x 10⁹/L

# Dexamethasone as Initial Treatment for ITP: Study Design

<table>
<thead>
<tr>
<th></th>
<th>Single-Center Study</th>
<th>Multi-Center Study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>95</td>
</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td>18-65</td>
<td>2-70</td>
</tr>
<tr>
<td><strong>Regimen</strong></td>
<td>Once per mo x 6 cycles</td>
<td>Biweekly x 4 cycles</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Assessed at Day 28 after completion of latest cycle</td>
<td>Assessed at Day 60 after treatment</td>
</tr>
<tr>
<td><strong>Rescue</strong></td>
<td>Prednisone 0.25 mg/kg/day</td>
<td>Dexamethasone 0.035 mg/kg/day</td>
</tr>
</tbody>
</table>

Single-Center Study: Response to High-Dose Dexamethasone

- Relapse-free survival: 97% at 6 mos, 58% at 50 mos
- <6 cycles: no impact on ORR

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Multicenter Study: Response to High-Dose Dexamethasone

- At 15 mos of follow-up, 5 relapses each among subjects who achieved CR or PR/MR

CR: n = 58 (64%)
PR or MR: n = 19 (21%)
NR: n = 13 (14%)

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Dexamethasone as Initial Treatment for ITP: Summary

- Both regimens
  - High initial response rate
- Monthly regimen
  - High attrition rate (responses), possibly less well-tolerated than biweekly regimen
- Biweekly regimen
  - Higher frequency and durability of (complete) response among younger patients (<18 yrs)
- Observations await confirmation in an expanded study

More Dex + Rituximab?

- Rituximab 1, 7, 14, 28
- Dex x 4 days 1, 15, 29
- N – 14
<table>
<thead>
<tr>
<th></th>
<th>Adults (N=7)</th>
<th>Children (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-R&amp;D Platelet Count</td>
<td>Median: 39k; Avg: 76k</td>
<td>Median: 42k; Avg: 32k</td>
</tr>
<tr>
<td># CR's after Initial Rituximab</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td># PR's after Initial Rituximab</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Avg Platelet change after Rituximab #1/Dex #1</td>
<td>85k Increase</td>
<td>109k Increase</td>
</tr>
<tr>
<td>Avg overall platelet change</td>
<td>149k Increase</td>
<td>81k Increase</td>
</tr>
</tbody>
</table>
Soo…

• Maybe you need more dex up front?
• Maybe you need to add rituximab?
• Maybe you need clinical trials?
  – NIH
  • Prednisone vs dex x 3
An Approach

• Dexamethasone 40mg x 4 repeat q14 x 4
  – Only dex exposure
  – Saves other agents
2nd Line

• Splenectomy
  • Oldest and most effective therapy
• Rituximab
  • Only 20% “cure” rate
• TPO agonist
Should Adults with SCC be Transfused?

- Phase II study
- Adults with SS disease
- Hbg < 9
- Normal neuro exam
- RCT to maintain Hbg > 2 over baseline
Results

• 20 vs 16 patients
• Adverse events
  – 1.2/pt in trans vs 4.1/pt in control
  – 5 hospitalizations vs 23
  – Crisis 0.7/pt vs 3.6/pt
  – Pulmonary complications 0 vs 25%
Transfusion in Sickle Cell

- Very promising but preliminary study
- Confirms clinical anecdotes
- Need large phase III trial!!
Reversal of Anticoagulants

- Lots of anecdotes
- Increasing data
Antiplatelet Agents

Aspirin
- Blocks thromboxane A₂ production
- Duration of effect: 5 – 7 days
- Tx: Desmopressin, platelet transfusions

Clopidogrel (Plavix)
- Blocks ADP receptor
- Duration of effect: 5-7 days
- Tx: Desmopressin(?), platelet transfusions(?), rVIIa (?)
Prasugrel (Effient)

- New thienopyridine
- Faster and more potent than clopidogrel
- Pro
  - Better outcomes with cardiac procedures
- Con
  - Bleeding!!!
  - Especially
    - CABG
    - Patients with history of stroke
    - Patients > age 75
    - Patients < 60 kg
Antiplatelet Agents

Glycoprotein IIb/IIIa inhibitors

• Abciximab (Reopro)
  • Duration: hours
  • Tx: Desmopressin, platelet transfusions

• Tirofiban (Aggrastat), Eptifibatide (Integrilin)
  • Duration: hours
  • Tx: Desmopressin, platelets, cryoprecipitate
“Heparins”

Standard heparin
  • Half-life: 1 hour
  • Protamine

LMW Heparin
  • Half-life: 4 hours
  • Protamine

Fondaparinux (Arixtra)
  • Half-life: 16-20 hours
  • Protamine ineffective!
  • rVIIa
Standard Heparin

- Rapid $T_{1/2}$ makes reversal unnecessary in most patients
- Protamine
  - Side effects
    - ~ 1% pulmonary hypertension
- Dose
  - < 30 mins: 1mg/100 units heparin
  - 30-60 mins: 0.5mg/100 units
  - 60-120 mins: 0.25 mg/100 units
LMW Heparin

• Protamine effective!
• 0-4 hours: protamine 1mg: 1mg enoxaparin then 4 hours later $\frac{1}{2}$ dose protamine
• 4-8 hours protamine 0.5 mg:1mg enoxaparin
• Other LMWH protamine 1mg:100 units
Protamine and LMWH

Thromb Haemost. 1990 Apr 12;63(2):271-4
Direct Thrombin Inhibitors

Argatroban
  • Half-life: 30 minutes

Bivalirudin (Angiomax)
  • Half-life: 40 minutes

Lepirudin (Refludan)
  • Half-life: 30 minutes - 100 hours

• Activated prothrombin complexes
• Dialysis for lepirudin
• rVIIa may not be effective
Warfarin Reversal

- General approach
- Patient risk factors
  - Bleeding
  - Thrombotic risk
- Level of INR
  - Risk of bleeding with INR > 6 varies from 0.6-4%
- Higher risk in older patients anticoagulated for arterial reasons
Vitamin K

• Both oral and IV very effective
  – PO "targeted" to liver
• Sub-q and IM not effective in RCT and should not be used!
• Lower doses (1-2.5 mg) effective and does not lead to warfarin resistance
• SLOW (~1 hour) infusions of vitamin K has very low incidence of anaphylaxis
• No "rebound" with reversal
Prothrombin Complex Concentrates

• In theory, ideal for warfarin reversal

• However, all PCC in US are only “3-factor” concentrates

• 4-factor PCC available elsewhere and undergoing study in US
Guidelines

• INR 4.5-10 and not bleeding:
  – Vit K 1 mg po or
  – Hold warfarin (may take up to 36 hours to see effect)

• INR > 10 and not bleeding:
  – Vit K 2.5 mg po
Guidelines

• INR 4.5-10 and bleeding
  – Vit K 2.5-5 mg po or IV
  – Plasma (15 ml/kg)
• INR > 10 and bleeding
  – Vit 5-10 mg IV
  – Plasma (15 ml/kg)
When things don't go well...
rVIIa

- Widely used and recommended to reverse warfarin
  - Will rapidly lower INR
- But does it improved hemostasis?
Exploratory study on the reversal of warfarin with rFVIIa in healthy subjects

The Study

• DBRCT phase 1 trial assessed safety and effects of rFVIIa vs placebo in reversing warfarin-induced changes in hemostasis
• 12 patients warfarin
• 85 patients dose escalation of rFVIIa (5-80ug/kg)
The Study

• Outcomes
  – Bleeding from punch biopsy
  – INR, PT, aPTT
  – Thrombin generation
  – Thromboelastography
Coagulation Test

- INR, PT, aPTT normalized with rVIIa
- Example
  - Before: 1.1 ± 0.1
  - Warfarin: 2.8 ± 0.2
  - 80 µg/kg rFVIIa: 1.2 ± 0.1
TG parameters in the placebo or 80-μg/kg groups in experiment 2


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FTEG parameters in the placebo or 80-μg/kg groups in experiment 2

Mean bleeding duration before and after warfarin and trial product (rFVIIa or placebo) treatments for subjects in experiment 2

<table>
<thead>
<tr>
<th>Blood loss, mL</th>
<th>No.</th>
<th>Baseline (B0), mean ± SD</th>
<th>After warfarin treatment (B1), mean ± SD</th>
<th>After rFVIIa or placebo treatment (B2), LSM (CV)</th>
<th>Ratio of means at B2 (rFVIIa vs placebo)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>2.4 ± 1.1</td>
<td>3.8 ± 2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>24</td>
<td>4.0 ± 2.4</td>
<td>5.6 ± 2.2</td>
<td>4.7 (0.5)</td>
<td>1.2</td>
<td>.392</td>
</tr>
<tr>
<td>5 µg/kg</td>
<td>6</td>
<td>4.9 ± 2.5</td>
<td>9.7 ± 6.5</td>
<td>5.6 (0.5)</td>
<td>1.2</td>
<td>.392</td>
</tr>
<tr>
<td>rFVIIa10 µg/kg</td>
<td>6</td>
<td>4.3 ± 1.7</td>
<td>6.1 ± 2.6</td>
<td>4.0 (0.5)</td>
<td>0.9</td>
<td>.447</td>
</tr>
<tr>
<td>rFVIIa20 µg/kg</td>
<td>13</td>
<td>4.0 ± 2.3</td>
<td>4.9 ± 3.1</td>
<td>5.6 (0.5)</td>
<td>1.2</td>
<td>.225</td>
</tr>
<tr>
<td>rFVIIa40 µg/kg</td>
<td>12</td>
<td>4.5 ± 2.0</td>
<td>4.9 ± 1.8</td>
<td>5.9 (0.5)</td>
<td>1.3</td>
<td>.150</td>
</tr>
<tr>
<td>rFVIIa80 µg/kg</td>
<td>24</td>
<td>3.8 ± 2.3</td>
<td>5.3 ± 2.4</td>
<td>5.3 (0.5)</td>
<td>1.1</td>
<td>.312</td>
</tr>
</tbody>
</table>
Conclusion

• rVIIa was not effective in reversing warfarin anticoagulant effect
Other Studies

- Tanaka – rVIIa did not improve rat thrombin generation
Other Studies

- Dicknnette – PCC but not rVIIa effective in bleeding swine model
PPCs to the Rescue?

• 4-factor PCC have all Vit k prothrombotic factors
  – Prefect antidote to warfarin
• Not available in USA!!!
  – Only “3-factor” – missing VII
Dose VIIa Matter?

- Only need 10%
- Raraport showed X and II key to warfarin effect

Mechanism of the Anticoagulant Effect of Warfarin as Evaluated in Rabbits by Selective Depression of Individual Procoagulant Vitamin K–dependent Clotting Factors

Ariella Zivelin, L. Vijaya Mohan Rao, and Samuel I. Rapaport
Departments of Medicine and Pathology, University of California, San Diego, California 92093
New OHSU Protocol

- Intracranial hemorrhage:
- 4000 units PCC + 1mg of rVIIa
rVIIa – Bloom off the Rose?
Use of recombinant factor VIIa in US military casualties for a five-year period.

rVIIa

- Leading use is for massive bleeding
- Large use in US combat operations past 5 years
- 75% of US trauma centers recommend rVIIa
  - 22% of US massive transfusions received rVIIa
- Two RCT suggestive rVIIa reduced transfusions and did not increase complications
rVIIa

- N = 2,050 causalities who received transfusions
  - 506 (25%) received rVIIa
- Patients were sicker who received rVIIa
- Guidelines not followed
### TABLE 3. Percentage of AIS ≥ 3 for Various Body Regions for Patients Who Were Not Treated and Treated With rFVIIa

<table>
<thead>
<tr>
<th>Body Region</th>
<th>No rFVIIa (n = 1,544)</th>
<th>rFVIIa (n = 506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>22</td>
<td>33*</td>
</tr>
<tr>
<td>Face</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Chest</td>
<td>25</td>
<td>33*</td>
</tr>
<tr>
<td>Abdomen</td>
<td>16</td>
<td>32*</td>
</tr>
<tr>
<td>Extremity</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

* Significantly different at $p < 0.005$.

### TABLE 4. Demographic, Admission, and Laboratory Variables of Patients Not Treated and Treated With rFVIIa

<table>
<thead>
<tr>
<th>Variable</th>
<th>No rFVIIa (n = 1,544)</th>
<th>rFVIIa (n = 506)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24 (21–28; 1,534)</td>
<td>24 (21–28; 1,534)</td>
</tr>
<tr>
<td>ISS</td>
<td>17 (10–26; 1,542)</td>
<td>25* (17–34; 506)</td>
</tr>
<tr>
<td>GCS score</td>
<td>15 (13–15; 1,373)</td>
<td>14* (3–15; 468)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>118 (99–136; 1,387)</td>
<td>115* (86–133; 457)</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>66 (52–79; 1,366)</td>
<td>62† (44–77; 449)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>101 (81–122; 1,410)</td>
<td>112* (89–132; 470)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>98 (97.2–99.1; 857)</td>
<td>98 (97.1–99; 264)</td>
</tr>
<tr>
<td>BD (mmol/L)</td>
<td>4 (2–7; 888)</td>
<td>6* (3–12; 339)</td>
</tr>
<tr>
<td>INR</td>
<td>1.3 (1.1–1.5; 883)</td>
<td>1.4* (1.2–1.9; 333)</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>12.3 (10.5–13.9; 1,164)</td>
<td>11.7† (10.0–13.4; 410)</td>
</tr>
</tbody>
</table>

Significantly different at * $p < 0.0001$ and at † $p < 0.005$.

Values are medians with the interquartile range and number of patients in parentheses.
### TABLE 7. The Mortality Rate for the Overall Patient Population and After Propensity Analysis for Patient Treated or Not Treated With rFVIIa

<table>
<thead>
<tr>
<th>Overall</th>
<th>6 h (%)</th>
<th>24 h (%)</th>
<th>30 d (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No rFVIIa (n = 1544)</td>
<td>7.4</td>
<td>8.5</td>
<td>10.8</td>
<td>11.7</td>
</tr>
<tr>
<td>rFVIIa (n = 506)</td>
<td>10.9*</td>
<td>13.6*</td>
<td>22.3*</td>
<td>23.5*</td>
</tr>
<tr>
<td>Propensity matched</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No rFVIIa (n = 266)</td>
<td>6.8</td>
<td>9.4</td>
<td>13.5</td>
<td>14.3</td>
</tr>
<tr>
<td>rFVIIa (n = 266)</td>
<td>10.5</td>
<td>11.6</td>
<td>18.8</td>
<td>19.9</td>
</tr>
</tbody>
</table>

* Significantly different at $p < 0.01$. 
rVIIa

- Increased mortality even matching for equally injured controls
- Similar to in press OHSU findings in head trauma
rVIIa

- Great for hemophilia
- Disturbingly no studies showing benefit in other populations
- Clinical trials halted
- Need to re-evaluate promiscuous off-label use