New Treatment Options in the Management of Sepsis

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Objectives

- Understand a model of sepsis pathophysiology
- Review the Phase III clinical trial of drotrecogin alfa (activated)
- Outline key points in the development of guidelines for use of drotrecogin
- Discuss indications and contraindications of drotrecogin use
If you Pneumo like I knew Mo

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Physical Exam: T= 38.9°C (102°F), HR 121, RR 32 breaths, BP 80’s
CXR RLL infiltrate (breath sounds reduced over right lung)

WBC count, 2,500 cells/mm$^3$
Lactate level 3.2 mmol/L and patient is acidotic

PaO$_2$, 52 mm Hg on room air FiO2 = 0.21; PaO2/FiO2 = 247
Platelet count, 95,000 cells/mm$^3$
An empiric regimen of cefuroxime and erythromycin was initiated. The patient was admitted to the intensive care unit (ICU); his respiratory condition subsequently worsened, requiring intubation.

What SIRS criteria are present?

What acute organ failures are present?

Is there a source for suspected infection?

Would this patient be a likely candidate for treatment with drotrecogin?
Sepsis Facts

- >750,000 severe sepsis cases annually in US
  - Increasing problem
  - ~10% of ICU admissions
  - ~30-50% mortality rate

- Most common cause of death in non-cardiac ICU
  - 215,000 in U.S. annually
  - 600 deaths/day

- ~$16.7 billion in annual hospital costs*

Mortality of Sepsis Increases with Age in the US

![Graph showing the increase in sepsis mortality with age, with or without comorbidity.](chart.png)

*Angus et al. Crit Care Med 2001;29:1303-10*
Definitions in Sepsis

Systemic Inflammatory Response Syndrome (SIRS)
- ≥ 2 of the following criteria:
  - Temperature >38°C or <36°C
  - Heart rate >90 bpm
  - Respiratory Rate >20 bpm or PaCO₂ <32 torr
  - WBC >12,000, <4,000 or >10% bands

Sepsis
- SIRS + infection

Severe Sepsis
- Sepsis with organ dysfunction, hypoperfusion or hypotension

Septic Shock
- Sepsis with hypotension and perfusion abnormalities despite adequate volume resuscitation

Relationship Between SIRS, Sepsis and Severe Sepsis

- Bacteria
- Virus
- Fungus
- Infection
- SIRS
- Pancreatitis
- Trauma
- Burns

Severe Sepsis

Shock

Evolution of Sepsis
Inflammation, Endothelial Injury, & Clotting

- Localized Infection
  -> 
  Toxin Release
  -> 
  Inflammatory Cytokines

  
  Activated Neutrophils

  
  Endothelial Injury
Coagulation Imbalance in Sepsis

**ANTICOAGULANTS:**
- Thrombomodulin
- Activated Protein C & S
- Tissue-type Plasminogen Activator (tPA)
- Prostacyclin
- EDRF (NO)
- Antithrombin
- Tissue Factor Pathway Inhibitor

**PROCOAGULANTS:**
- Tissue Factor
- Plasminogen Activator Inhibitor 1 (PAI-1)
- Platelet Activating Factor
- Von Willebrand Factor
- Fibronectin

**NET RESULT:** HYPERCOAGULATION

Sepsis Pathways

Inflammatory Process

- TAFI-Thrombin Activatable Fibrinolysis Factor
- PAI-1- Plasminogen Activator Inhibitor 1
- TNF- Tumor Necrosis Factor

Clotting Process

- Coagulation cascade
- Thrombin
- Factor VIII
- Factor Va
- Inactivation

Fibrinolytic Process

- Activated protein C
- PAI-1
- Suppression of fibrinolysis

Bacterial, viral, fungal, or parasitic infection or endotoxin
Therapeutic Strategies

Supportive Tx:
- Antimicrobials
- Inotropes
- Vasopressors
- Fluid/nutrition
- Mech Ventilation
- Surgery

Outcome: Standard Tx
- 30-50% mortality
- Significant morbidity

Investigational Adjunctive Tx:
- Corticosteroids
- Moab to endotoxin
- TNF antagonists
- IL antagonists
- Anti-Thrombin III
- TFP Inhibitor
- Drotrecogin alfa ac.
Development of Drotrecogin Alfa (activated)

- 1960’s antithrombic activity of Activated Protein C named
- 1980’s Human Activated Protein C cloned
- 1994 - First human dose of rhAPC
- 1996 - Phase 2 study initiated
- 1998 - Phase 3 study initiated
  - July 2000: Study terminated early at second interim analysis
- 2001 – Xigris approved by FDA
Inclusion Criteria:
- Known or suspected infection
- ≥ 3 of the SIRS criteria
- ≥ 1 acute (< 24hr in duration) organ failures

Primary Endpoint: All-Cause Mortality at 28 days

n=2,280 (study ended early after second interim analysis n=1,690)

Placebo
96 hr infusion + standard treatment

Drotrecogin
24 mcg/kg/hr 96 hour infusion + standard treatment

PROWESS: Exclusion Criteria

- < 18 years of age
- > 135 Kg
- Platelet count <30,000/mm³
- Pregnancy, breastfeeding
- Medications that increase risk of bleeding
- Patient expected to die within 24h
- Neutropenia
- Organ transplant recipients
- Known hypercoagulable state
- CRF/dialysis
- Chronic liver failure

- History within previous 3 months of severe head trauma requiring hospitalization, intracranial surgery, or stroke
- History of intracerebral arteriovenous malformation, cerebral aneurysm, or CNS mass lesion
- Anticipated need for epidural during study drug infusion

Medication Exclusions – Increased Bleeding Risk

- UFH dose > prophylaxis within 8h of infusion
- LMWH dose > prophylaxis* within 12h of infusion
- ASA ≥ 650 mg/d ≤ 3d before study
- GP 2b3a ≤ 7d before study

- Fibrinolytic ≤ 3d before study
- AT III ≥ 10,000 U ≤ 12h before study
- Protein C ≤ 24h before study
- Warfarin (≤ 7d before study and PTT > upper limit of normal)

* as specified in the package insert

PROWESS: Population

Baseline characteristics/demographics well-matched

- Site, type, and gram stain class of infection
  - Pulmonary and intra-abdominal most common
  - Gram +/- occurred at similar rates

- Organ failure at entry
  - 75% with ≥ 2 organ failures
  - Shock and mechanical ventilation status

Site of Infection

- Lung: 53.6%
- Abdominal: 19.9%
- Urinary: 10.3%
- Other: 16.3%

Legend:
- Yellow: Placebo
- Red: Drotrecogin

Percent Incidence
Type of Infection

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Placebo</th>
<th>Drotrecogin alfa (activated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gm +</td>
<td>25.8%</td>
<td>36.8%</td>
</tr>
<tr>
<td>Gm -</td>
<td>21.8%</td>
<td>32.7%</td>
</tr>
<tr>
<td>Mixed</td>
<td>15.6%</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td></td>
<td>36.8%</td>
</tr>
<tr>
<td>Positive Blood</td>
<td></td>
<td>32.7%</td>
</tr>
</tbody>
</table>

PROWESS Results
Primary Stratified Intention-to-Treat Analysis

28 Day All-Cause Mortality

Placebo: 30.8% (n=850)
Drotrecogin alfa (activated): 24.7% (n=840)

p=0.0054

6.1% ↓ in absolute mortality
19.4% ↓ in RR (Relative Risk) of death

28-Day All-Cause Mortality
Kaplan-Meier Survival Curve

Days from Start of Infusion to Death

Percent Survivors

Drotrecogin alfa (activated)
(n=850)

Placebo
(n=840)

p=0.006 (stratified log-rank test)

US Patients Had Better Response

- International protocol data may have diluted US mortality benefit
- More benefit in U.S.-treated patients leads to issues of supportive therapy

http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Anti-Infective
PROWESS: Subgroup Analysis

Mortality Rates by:
- Gender
- Age
- Origin
- Disease Severity
- Infection site and type

- APACHE II Score
- Baseline status
  - Protein C deficiency
  - AT III deficiency
  - IL-6 levels

Subgroups not powered to detect differences

Mortality Rates by Number of Organ Failures at Baseline

Mortality as a Function of APACHE II at Study Entry

APACHE Quartile

28-Day Mortality Rate

0% 10% 20% 30% 40% 50% 60%

1st 2nd 3rd 4th

Placebo  Drotrecogin alfa (activated)

0.12 0.15 0.26 0.22

0.36 0.24

0.49 0.38

http://www.fda.gov/ohrms/dockets/ac/cder01.htm#Anti-Infective
## Mortality as a Function of APACHE II Quartiles

<table>
<thead>
<tr>
<th>APACHE II Quartiles (score)</th>
<th>rhAPC (850) Mortality (%)</th>
<th>Placebo (840) Mortality (%)</th>
<th>Mort Diff (%)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1+Q2 (&lt;25)</td>
<td>82/436 (19)</td>
<td>83/437 (19)</td>
<td>0</td>
<td>0.99</td>
<td>0.75, 1.30</td>
</tr>
<tr>
<td>Q3+Q4 (25-53)</td>
<td>128/414 (31)</td>
<td>176/403 (44)</td>
<td>-13</td>
<td>0.71</td>
<td>0.59, 0.85</td>
</tr>
</tbody>
</table>
**Effect of time to treat on survival**

Mean time was 16 hours

**28-day Mortality (%)**

<table>
<thead>
<tr>
<th>Hours to administration by quartile</th>
<th>Placebo</th>
<th>Drotrecogin alfa (activated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-17.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.8-22.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;22.5</td>
<td></td>
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</table>

* Placebo
* Drotrecogin alfa (activated)  

Quantities:  
- **n = 1,690**  

Serious Bleeding Events

- intracranial hemorrhage
- life threatening
- require ≥ 3 units of PRBC/day for 2 consecutive days

# Comparative Number Needed-to-Treat

<table>
<thead>
<tr>
<th>Agents</th>
<th>Observed Number Needed-to-Treat (NNT) to save an additional life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drotrecogin alfa (activated) in PROWESS Severe Sepsis (28-Day Mortality)</td>
<td>16*</td>
</tr>
<tr>
<td>Streptokinase vs. Placebo in ISIS-2 Acute MI (35-day mortality)</td>
<td>36</td>
</tr>
<tr>
<td>tPA vs. Streptokinase in GUSTO Acute MI (30-day mortality)</td>
<td>100</td>
</tr>
</tbody>
</table>

* US Patients NNT = 11

* APACHE 3 & 4 quartiles NNT = 8

Drotrecogin alfa (activated) significantly reduces mortality in severe sepsis patients with acute organ dysfunction - 1 life saved for every 16 patients treated

Incidence of serious bleeding events not statistically different from placebo in 28 day study period
Unanswered Questions

- Duration of administration?
- Use in patients with risk of bleed?
- Mild-moderate sepsis?
- Immunocompromised?
- Use in patients with renal or liver failure?
- Do patients have to be in the ICU?
- Who can prescribe the drug?
Patient Location on Day 28

PROWESS

% of Patients

- ICU-Vent: 9.5%
- ICU-No Vent: 4.3%
- Floor: 30.6%
- Skilled Nursing Facility: 11.4%
- Home-Support: 19.4%
- Home-No Support: 24.8%

Results NS

Functional Status on Day 28

PROWESS

Placebo (n=568)  Drotrecogin alfa (activated) (n=629)

Number of Dependencies

% of Patients

Time to Resolution of Cardiovascular Organ Dysfunction

- Patients with CV organ dysfunction at baseline
- Non-survivors censored at the time of death

- Placebo (n=736)
- Drotrecogin Alfa (activated) (n=746)

(1.3 more vasopressor-free days)
(1.1 more respirator-free days)

p=0.009

PROWESS Morbidity

Preliminary Conclusions

- **More survivors**
  - Faster resolution of cardiovascular and respiratory dysfunction
  - No difference in
    - Organ failure scores
    - Duration and intensity of care
    - Functional and discharge status of survivors

- **No morbidity penalty**

*Angus et al. Crit Care Med (in press)*
Patient Selection Criteria

- PROWESS inclusion criteria
  - Known or suspected infection
  - ≥ 3 of SIRS criteria
  - ≥ 1 acute (<24hr in duration) organ failures

- PROWESS exclusions - contraindications vs. warnings

- Site specific guidelines
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- **ORGAN DYSFUNCTION CRITERIA**
  - § Cardiovascular: SBP <90 mm Hg or MAP <70 mm Hg for at least one hour despite adequate fluid resuscitation, adequate intravascular volume status or use of vasopressors in an attempt to maintain a systolic blood pressure of >90 mm Hg or a mean arterial pressure of >70 mm Hg
  - § Kidney: UO <0.5 ml/kg/hour for >1 hour, despite adequate fluid resuscitation
  - § Respiratory: PaO₂/FiO₂ <250 in the presence of other dysfunctional organs or systems or <200 if the lung was the only dysfunctional organ
  - § Hematologic: Platelet <80,000/mm³ or decreased by 50 percent in the 3 days preceding enrollment
  - § **Unexplained metabolic acidosis:** pH <7.30 or the base deficit had to be >5.0 mmol/liter in association with a plasma lactate level that was >1.5 times the upper limit of the normal value