Current FDA Considerations on Pathogen Reduction

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Merits of the Current Approach of Donor Screening and Testing

Advantages
• No toxicity issues for recipients of products
• Detection is specific for particular agents
• New methods can be developed for novel and emerging pathogens

Disadvantages
• For certain pathogens detection is not 100% successful
  – Bacteria
  – Protozoa
  – Viral (window period)
• Development of detection methods for novel and emerging pathogens would be delayed due to lack of knowledge about the pathogen
• Additional tests for emerging pathogens increase cost
**Merits of Pathogen Reduction Technology as an Alternative to Donor Screening and Testing**

**Advantages**
- Shown effective against many organisms including some emerging pathogens
- May prevent GVHD and other wbc related adverse events

**Disadvantages**
- May not be effective against all organisms
- May not be 100% effective even against sensitive pathogens
- Current technologies are not applicable to all types of transfusion products
- May have toxicity due to residual compounds
- May damage the transfusion product
- May lead to alloimmunization by neoantigens
- May cause unexpected adverse events
Recommendation of the HHS Advisory Committee on Blood Safety and Availability (ACBSA) Regarding Pathogen Reduction

• At a meeting in January 2008 the ACBSA recommended that the Department should:
  “Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implementation as they become available”
• FDA fully supports the ACBSA recommendation through its evaluation of Pathogen Reduction Technologies
Benefits of Pathogen Reduced Products Should Outweigh the Risks

Benefit =

Reduction of Current risks:

- HTLV 1/2,993,000
- HIV 1/2,135,000
- HCV 1/1,930,000
- WNV 1/350,000
- HBV 1/277,000
- Sepsis 1/86,000

Reduction of future risks:

- Emerging pathogens 1/????

Tolerable Risk
Toxicity, adverse events should be much less than the expected benefits << 1/86,000

Determination of the Risks Associated with Pathogen Reduced Components

- Pre-clinical evaluation
- Clinical trials in healthy volunteers
- Pivotal evaluation of efficacy and safety through clinical trials in transfused patients
  - Prospective, randomized, blinded clinical trials of PR treated vs. conventional transfusion products
    - Platelets
    - Red cells
    - Plasma
Phase III Clinical Trials of Pathogen Reduced Red Cell Products

Cerus S303 and Vitex pen 110

- Patients developed antibodies to treated red cells
- Both sponsors voluntarily halted their trials

Benjamin, R.J., ISBT Science Series (2006) 1, 222-226
Clinical Endpoints that Reflect Efficacy and Safety of a Platelet Transfusion Product

• Efficacy
  – Transfusion response (corrected count increment, (CCI)
  – Transfusion frequency
  – Bleeding Frequency (Grades 2-4)

• Safety
  – Adverse events
  – Alloimmunization
Clinical Trials of PR Platelets in Thrombocytopenic Patients

• Prospective studies
  – Sprint and Eurosprite trials (Cerus)
  – Hovon 86 (Dutch Blood Service)
  – Mirasol trial (Caridian)

• Surveillance studies on routine use of PR platelets
  – France and Belgium
Pathogen Reduced Platelets Have Lower Corrected Count Increments (CCI)

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Patients in study</th>
<th>% of plasma stored platelets CCI at 1 hr</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRINT</td>
<td>645</td>
<td>-31%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HOVON</td>
<td>184</td>
<td>-31%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MIRASOL</td>
<td>118</td>
<td>-31%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

1 = UVA/psoralen 2 = UVB/riboflavin

c = Goodrich et al. Transfusion, May 2010
## Hemostatic Efficacy for UV A/psoralen (Intercept) Treated Platelets

<table>
<thead>
<tr>
<th><strong>SPRINT</strong> study</th>
<th>Control platelets</th>
<th>Pathogen reduced platelets</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of pts with Grade 2 bleeding</td>
<td>58.5%</td>
<td>57.5%</td>
<td>NS for inferiority</td>
</tr>
<tr>
<td>Days of Grade 2 bleeding</td>
<td>2.5</td>
<td>3.2</td>
<td>0.023</td>
</tr>
<tr>
<td>% patients with Grade 2-4 bleeding</td>
<td>34</td>
<td>43</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HOVON</strong> study</th>
<th>Control platelets</th>
<th>Pathogen reduced platelets</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with Grade 1-3 bleeding</td>
<td>19</td>
<td>32</td>
<td>0.034</td>
</tr>
</tbody>
</table>
## Hemostatic Efficacy for UVB/riboflavin (Mirasol) Treated Platelets

<table>
<thead>
<tr>
<th>MIRASOL study</th>
<th>Control platelets</th>
<th>Pathogen reduced platelets</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with Grade 2-4 bleeding</td>
<td>15</td>
<td>30</td>
<td>NS</td>
</tr>
</tbody>
</table>
Adverse Events Reported in the SPRINT Study

- 898 adverse event types were reported by blinded observers
- 11 adverse event types were different with statistical significance….all went against the treatment arm
- 4 of the 11 were clinically significant Grade 3 and 4 events:
  - Hypocalcemia, Syncope, Pneumonitis, Acute Respiratory Distress Syndrome (ARDS)

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75
# ARDS Rates in the Treatment vs. Control Arms of the SPRINT Study

Snyder E et al. Transfusion. 2005 Dec;45(12):1864-75

**Prospective and blinded evaluations during the clinical trial**

<table>
<thead>
<tr>
<th></th>
<th>Intersol (PR) platelets</th>
<th>Control platelets</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>318</td>
<td>327</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>5</td>
<td>0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Retrospective review of medical charts by a blinded expert panel**

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<th>Control Platelets</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>78</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Total Acute Lung Injury (ALI)</td>
<td>19 (6.0%)</td>
<td>16 (4.9 %)</td>
<td>0.60</td>
</tr>
<tr>
<td>ARDS</td>
<td>12 (3.8%)</td>
<td>5 (1.5%)</td>
<td>0.09</td>
</tr>
<tr>
<td>ALI, non-ARDS</td>
<td>7 (2.2%)</td>
<td>11 (3.4%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Can adverse event signals captured in a prospective, randomized, controlled and blinded study be evaluated through a passive adverse reporting study?

• France and Belgium have been using pathogen reduced platelets for several years
• Adverse events on transfused patients are reported through a passive hemovigilance reporting system
• Frequency of reporting of adverse events is much lower than what was reported in SPRINT trial
• There is no active control group to identify events specifically related to PR platelets
Comparison of Adverse Event Reporting in the SPRINT Trial vs. European Hemovigilance Studies

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<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Per transfusion</td>
<td>Per patient</td>
<td>Per transfusion</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2678</td>
<td>318</td>
<td>5106</td>
</tr>
<tr>
<td>% stem cell transplant patients</td>
<td>78</td>
<td></td>
<td>7.2</td>
</tr>
<tr>
<td>% of pts with any reaction</td>
<td>99.7</td>
<td>1.1</td>
<td>6.4</td>
</tr>
<tr>
<td>% of plt related reactions</td>
<td>3.0</td>
<td>26.0</td>
<td>0.8</td>
</tr>
<tr>
<td>% of plt with serious reactions</td>
<td>27.0</td>
<td>0.1</td>
<td>0.15</td>
</tr>
</tbody>
</table>
Summary and Conclusion

• Pathogen Reduction of labile blood products could improve blood product safety, especially for platelets, but should not add greater risks
  – Clinical trials with Pathogen Reduced red cells have demonstrated antibody generation
  – Clinical trials with Pathogen Reduced platelets have demonstrated decreased efficacy and associated adverse events including acute lung injury in the SPRINT trial.
  – These reports raise concern that the benefits of current pathogen reduction technologies may not outweigh the risks

• Further clinical trials of current technologies are needed to resolve FDA’s concerns over decreased efficacy and increased adverse events seen with Pathogen Reduced platelets