Transfusions, etc!

Thomas DeLoughery, MD MACP FAWM
Oregon Health & Sciences University
DISCLOSURE

Current Relevant Financial Relationship(s)
None
Contact Pathway

- Part of coagulation cascade everyone ignores
- Factors 11, 12, prekallikrein and HMW Kininogen
- No bleeding 12, prekallikrein and HMW Kininogen
Factor 11

- Deficient patients often with mild to no bleeding
- Less arterial and venous disease
Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events.
Contact Inhibition

- Contact pathway not need for routine hemostasis
- Blocking pathway in animal models show less thrombosis with no bleeding
- Human studies...
FXI-ASO

- Factor 11 antisense
- TKA N= 300
- Drug started 36 days before surgery
  - Days 1, 3, 5, 15, 22, 29, 36
- NEJM 372:232, 2014
### Results

<table>
<thead>
<tr>
<th></th>
<th>FXI 200mg</th>
<th>FXI 300mg</th>
<th>Enox 40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (%)</td>
<td>36</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Prox DVT (%)</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Bleeding (%)</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>F11 (%)</td>
<td>38</td>
<td>20</td>
<td>93</td>
</tr>
</tbody>
</table>
Bottom Line

• 2 proofs of concept
  – Antisense
  – Lower 11 with less clots and no more bleeding
Osocimab

- Mab binds F11 active site
- 2 phases – TKA N = 813
  - Phase 1 - day after surgery
    - 0.3, 0.6, 1.2, and 1.8 mg/kg
  - Phase 2 – day before surgery
    - 0.3, 1.8 mg/kg
- JAMA 323:130, 2020
## Results PostOp

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg/kg</th>
<th>0.6 mg/kg</th>
<th>1.2 mg/kg</th>
<th>1.8 mg/kg</th>
<th>Enox 40mg</th>
<th>Apix 2.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (%)</td>
<td>18</td>
<td>8</td>
<td>13</td>
<td>14</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>PDVT (%)</td>
<td>2.6</td>
<td>5.9</td>
<td>3.8</td>
<td>3.8</td>
<td>3.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>
## Results - PreOp

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg/kg</th>
<th>1.8 mg/kg</th>
<th>Enox 40mg</th>
<th>Apix 2.5 bid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE (%)</strong></td>
<td>23</td>
<td>9</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td><strong>PDVT (%)</strong></td>
<td>6.5</td>
<td>2.5</td>
<td>3.9</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>Bleeding (%)</strong></td>
<td>1.9</td>
<td>3.7</td>
<td>5.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Milvexian

- Oral F11 inhibitor
- TKA  N = 1242
- 6 doses tested
  - BID 25, 50, 100, 200 mg
  - qDay 25, 200mg
# BID Dosing

<table>
<thead>
<tr>
<th></th>
<th>25 mg</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
<th>Enox 40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE (%)</strong></td>
<td>21</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td><strong>PDVT (%)</strong></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
# qDay Dosing

<table>
<thead>
<tr>
<th></th>
<th>25 mg</th>
<th>50 mg</th>
<th>200 mg</th>
<th>Enox 40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (%)</td>
<td>25</td>
<td>24</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>PDVT (N)</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding (n)</td>
<td>0</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
Abelacimab

- Mab binds and locks F11 zymogen form
- TKR N = 412
- Drug started 4-6 after surgery
- 30, 75, 150 mg
- NEJM 385:609, 2021
# Results

<table>
<thead>
<tr>
<th></th>
<th>30 mg</th>
<th>75 mg</th>
<th>150 mg</th>
<th>Enox 40mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE (%)</td>
<td>13</td>
<td>5</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>PDVT (N)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bleeding (n)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Prophylaxis

• No increased risk of bleeding with blocking F11
• Higher doses more effective than enoxaparain
• Mab just one dose
• Phase III trials underway
Asundexian

• Oral F11 inhibitor
• Atrial Fibrillation N = 755
• Asundexain 20 or 50mg daily
• Apixaban 5 mg bid
• Lancet 399:1383, 2022
## Results

<table>
<thead>
<tr>
<th></th>
<th>20 mg</th>
<th>50 mg</th>
<th>Apix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td>0.8</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Bleeding</td>
<td>5</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
Bottom Line

• Contact pathway promise effectiveness with less bleeding
• Phase III studies underway
• Also effective for “surfaces”
  – Dialysis
  – ECMO
  – VADs
Platelet Refractoriness
I’m not just the president of Hair Club for Men...
Assessing Response To Platelet Transfusions

• Expected increment 15 minutes after Txn:
  - 5-7,000/uL for each random donor
  - 30,- 50,000/uL for each pheresis
<table>
<thead>
<tr>
<th>Measure of Transfusion outcome</th>
<th>Formula</th>
<th>Values s/o refractoriness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Count Increment (ACI)</td>
<td>(Post transfusion plt count – Pre transfusion plt count)</td>
<td>At 60 min ACI, &lt;5000/cumm after one unit of RDP</td>
</tr>
<tr>
<td>Corrected Count Increment (CCI)</td>
<td>(ACI x BSA m²) x 10¹¹ No. of plts transfused x 10¹¹</td>
<td>At 10-60 min &lt;5000/cumm</td>
</tr>
<tr>
<td>Posttransfusion Platelet Recovery (PPR)</td>
<td>ACI x Total blood volume x 100 No. of plts transfused</td>
<td>At 60 min &lt;30% At 24hrs &lt;20% (Normal at 1 hr: 67%)</td>
</tr>
</tbody>
</table>

BSA = Body surface area

AABB, Technical manual 16th Edn
Pavenski et al, Tissue antigens 2012

https://slideplayer.com/slide/5795610/
Poor Platelet Response

- Bum product
- Increased consumption
  - Sepsis, bleeding, fever, DIC
- Platelet refractoriness
  - Anti-HLA antibodies, etc.
Typical Platelet Transfusion Responses

- Intended Response: 65-85%
- Non-Immune Refractoriness: 10-30%
- Immune Refractoriness: 3-5%

Platelet Refractoriness

- Poor/no increment immediately after transfusion
- Only ~ 30% are due to anti-HLA antibodies
Other Cause Of Platelet Refractoriness

- Antiplatelet antibodies
- Heparin induced thrombocytopenia
- Drugs (Vancomycin)
- VOD/liver disease
- Post-transfusion purpura
Anti-HLA antibodies

- Platelets with HLA A and B antigens
- Occurs in
  - Previous pregnancies
  - Previous transfusions
- Some naturally occurring
Anti-HLA antibodies

• Risk factors
  – Pregnancy (32% vs 9%)
  – Disease
    • Higher in aplastic anemia and lower in lymphoid malignances
HLA Alloimmunization

• Occurs in 5-50% of patients
• Leads to profound platelet refractoriness
• Complicate therapy of cancer and surgeries
HLA Alloimmunization

- Does not respond to immunosuppression!
- Many therapies have been tried and found wanting
Diagnosis

• Demonstrate platelet refractoriness
• Demonstrate presence of anti-HLA antibodies
Panel Reactive Antibodies

- Patients serum is tested against a variety of HLA antigens
  - Many methods are used

- Panel Reactive Antibodies (PRA)
  - Based on anti-HLA antibodies and frequency in the population of those HLA antigens
**Example of Report**

![Example Report Image]

**HLA Antibody Screening Report with MFI**

**HLA Typing Results:**

<table>
<thead>
<tr>
<th>Name/ID</th>
<th>Relation</th>
<th>A</th>
<th>B</th>
<th>Bw</th>
<th>Cw</th>
<th>DR</th>
<th>DRw</th>
<th>DOB</th>
<th>DQA</th>
<th>DPB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
<td>26</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HLA Typings have been done by sequence-specific primers, reported as serological equivalents.

**Unacceptable Antigens Assigned in UNOS**

**HLA Antibody Screening Results:**

<table>
<thead>
<tr>
<th>Sample Date</th>
<th>Sample #</th>
<th>Test</th>
<th>Result</th>
<th>PRA (%)</th>
<th>Specificities</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/11/2019</td>
<td>19892460</td>
<td>LUM ID 1</td>
<td>Positive</td>
<td>B:51 53 35 78</td>
<td></td>
</tr>
</tbody>
</table>
Example of Report

MFI values for single antigen specificities identified. MFI values of 1000 and greater are considered as positive.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Allele</th>
<th>MFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>B51,Bw4</td>
<td>B*51:01</td>
<td>7994</td>
</tr>
<tr>
<td>B51,Bw4</td>
<td>B*51:02</td>
<td>4210</td>
</tr>
<tr>
<td>B53,Bw4</td>
<td>B*53:01</td>
<td>4154</td>
</tr>
<tr>
<td>B35,Bw6</td>
<td>B*35:01</td>
<td>4114</td>
</tr>
<tr>
<td>B78,Bw6</td>
<td>B*78:01</td>
<td>3917</td>
</tr>
</tbody>
</table>

Comments:
Platelet Refractory Panel
Fax Report to OHSU Transfusion Services 503-494-4144
Fax Report to ARC HLA Lab 503-280-1483

Estimated cPRA = 31%, based on >3000 MFI cutoff
Transfusion Strategies

• Sounds simple “Pick product not likely to react”
• Difficult in practice
• Methods
  – HLA matching
  – HLA avoidance
  – Cross-matching
HLA Matched Platelets

- Picking platelet unit match for patients HLA type
- Platelet donors with HLA typing on file
- Can take time
Match grades for HLA-matched platelets

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ANTIGEN MATCHES</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4 antigen match</td>
</tr>
</tbody>
</table>
| B     | 2 or 3 antigen match  
Unmatched antigens are unknown or cross-reactive |
| B1U   | 1 antigen unknown or blank |
| B1X   | 1 cross-reactive group |
| B2UX  | 1 antigen blank and 1 antigen cross-reactive |
| B2X   | 2 antigens cross reactive |
| C     | 1 mismatched antigen |
| D     | 2 or more mismatched antigens |

Grade A is the ideal match. Some B grade matches such as B1U or B2U can provide an adequate response, however grade C and D matches do not provide a better
HLA Avoidance

• Picking platelets they don’t have implicated HLA antigens
• Faster and can use products off the shelf
Example of Report
Platelet Crossmatching

- Using patients serum to rule out reacting products
- Can screen a wide number of platelets
Pros-Cons

• HLA matching
  – Pro: prevents more HLA issues
  – Con: hard to get good matches

• HLA avoidance
  – Pro: more donors
  – Con: risk more antibodies

• Cross matching
  – Pro: rapid
  – Con: risk of more antibodies
Work Flow at OHSU

Patient not responding to platelets

Calculate CCI on 10-60 minute post-transfusion platelet count

Greater than 5,000-7,500: not platelet refractory

Give random platelets

Patient has HLA antibodies with cPRA <20%

Give random platelets

Less than 5,000-7,500: patient may be platelet refractory

Test patient for HLA Abs and HLA type

Patient has HLA antibodies with cPRA >20%

Give HLA matched or Ag Neg platelets

If not responding, consider additional testing

If not responding, consider other causes
Really Refractory

- Review for “good” donors
- Consider family members
- Review if other causes of refractoriness
Heroic Therapy

• Platelet drips
  – One unit over 6 hours
• High dose IVIG
  – 1 gram/kg twice weekly
• Plasmapheresis
• rVIIa
• TPO-agonists
Platelet Drips

- Minimal rise in platelets
- But cessation of bleeding
  - Some platelets survive for hemostasis
- Anecdotal
- Clinical trial underway
IVIG

- May improved 1 hours increment
- No effect on 24 hours
- Negative clinical trials
- Not recommended
rVIIa

- Recombinant factor VIIa effective in some platelet disorders
- Use is anecdotal
- Consider if life-threatening bleeding
Platelet Growth Factors

- Not effective for chemotherapy
- Can be considered in thrombocytopenic liver patients before transplant
Others

• Plasmapheresis
  – Risky

• Eculizumab
  – ~ 50% response rate in small study
  – Very expensive and minimal data
Prevention!

- Need white cells plus platelets to get alloimmunization
- Leukodepletion markedly reduces alloimmunization
TRAP Trial: Alloimmunization

New Eng J Med 1997; 337:1861-9
TRAP: Refractoriness

Leukoreduction

• Prestorage for all blood products
  – > 70% reduction in alloimmunization

• Not perfect to prevent all alloimmunization
  – Pregnancy
  – Spontaneous
  – Even with leukoreduction some patients become alloimmunization
Platelet Refractoriness

- Consumption vs immune destruction
- Prevention is key
- Difficult clinical issue