Update: Bleeding

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@bloodman
DISCLOSURE

Relevant Financial Relationship(s)
Speaker’s Bureau – none
Talk

• New and future options for bleeding
  – Von Willebrand Disease
  – Hemophilia
Classification of VWD

- **Type 1**: Low concentrations of normal protein (quantitative defect) (80%)
- **Type 2**: Abnormal proteins (qualitative defect)
  - 2A: Failure to form HMW multimers
  - 2B: Enhance binding to GP 1b
  - 2N: Abnormal factor VIII binding site
- **Type 3**: No VWF
- **Platelet type pseudo-VWF**
- **Acquired defects**
Treatment by Types

- Type 1: DDAVP, VIII/vWF Concentrate
- Type 2A: DDAVP (10%) VIII/vWF Concentrate
- Type 2B: VIII/vWF Concentrate
- Type 2N: VIII/vWF Concentrate
- Type 3: VIII/vWF Concentrate
- Platelet type: ???
- Tranexamic acid useful adjunct!
rVWF

- Products like Humate-P are VIII/VWF concentrates
- rVWF (Vonvendi) is just rVWF
  - No VIII!
- Need one dose of rVIII with first dose of rVWF
  - Or start a day before surgery
- Not for emergency bleeding!
2021 VWD guidelines on *diagnosis*

- Panel suggests using the newer assays of VWF activity that evaluate platelet binding (e.g. VWF:GPIbM, VWF:GPIbR) over the VWF:RCo assay.

- Use a VWF level of <0.3 regardless of bleeding and <0.5 if + bleeding (ABO specific ranges are not needed).

- *For people who have historical type 1 VWD but now have normal levels, reconsider the diagnosis but don’t necessarily remove it*.

- For type 2B, use genetic testing over the RIPA test.

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2021 VWD guidelines on management

- For patients with VWD and severe and frequent bleeds, long-term prophylaxis is suggested
- DDAVP challenges should be done for those who will likely respond (note Stimate is still not available) (could maybe skip it for adults if levels >0.30)
- DDAVP contraindications: active CV disease, seizure disorders, type 1C and surgery, type 2B, pre-eclampsia
- For surgeries: get FVIII and VWF levels >0.5 for at least 3 days

2021 VWD guidelines on management

- For minor surgery, get levels over 0.5 AND use TXA
- Type 1 VWD with VWF >0.3 and mild bleeding phenotype, just give TXA for minor mucosal procedures
- Use TXA or oral hormonal pill for heavy menstrual bleeding rather than DDAVP
- For women with VWD and who are pregnant and need an epidural, get levels 0.5-1.5
- Give women TXA during post-partum period
Hemophilia

- Extended half-life products
- Emicizumab
- Gene therapy
Hemophilia A (VIII)

- Most common (~80%)
- Sex-linked
- 30% of patients have inhibitors
- Prophylaxis is standard
  - Prevents joint damage
  - Improves quality of life
Bleeding Rate
Episodic versus Prophylactic

<table>
<thead>
<tr>
<th></th>
<th>Annualized bleeding rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint bleeding</td>
<td>10</td>
</tr>
<tr>
<td>Other Bleeding</td>
<td>16</td>
</tr>
</tbody>
</table>

## Prophylaxis Guidelines

<table>
<thead>
<tr>
<th>Prophylaxis intensity</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose prophylaxis</td>
<td>25-40 IU FVIII/kg every 2 days</td>
<td>40-60 IU FIX/kg twice per week</td>
</tr>
<tr>
<td>Intermediate-dose prophylaxis</td>
<td>15-25 IU FVIII/kg 3 days per week</td>
<td>20-40 IU FIX/kg twice per week</td>
</tr>
<tr>
<td>Low-dose prophylaxis</td>
<td>10-15 IU FVIII/kg 2-3 days per week</td>
<td>10-15 IU FIX/kg 2 days per week</td>
</tr>
</tbody>
</table>

(with escalation of dose intensity, as needed)

Carcao et al, *Haemophilia* 2020
### Hemophilia A: Standard FVIII Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Half-life (hours)*</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard half-life products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advate</td>
<td>9 to 12</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Hemofil M</td>
<td>15</td>
<td>Plasma-derived; mAb-purified</td>
</tr>
<tr>
<td>Kogenate FS</td>
<td>11 to 15</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Koate (previously called Koate DVI)</td>
<td>16</td>
<td>Plasma-derived; chromatography purified</td>
</tr>
<tr>
<td>Kovaltry</td>
<td>12 to 14</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Novoeight</td>
<td>8 to 12</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Nuwiq</td>
<td>12 to 17</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Recombinate</td>
<td>15^A</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Xyntha</td>
<td>8 to 11</td>
<td>Recombinant</td>
</tr>
</tbody>
</table>
Factor VIII Dosing

- \((\text{Desired Factor VIII concentration} - \text{current level}) \times \text{weight (kg)}\)
  \(\frac{2}{2}\)

- \((\text{level desired}/2)\times \text{kg}\)

- Bad Bleed: 50 units/kg
### Extended Half-Life FVIII Products

<table>
<thead>
<tr>
<th>FVIII EHL product</th>
<th>B-domain modification</th>
<th>Additional modifications</th>
<th>Half-life (hrs, mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afstyla</td>
<td>Yes (truncated)</td>
<td>Single-chain</td>
<td>14.2 +/- 3.7</td>
</tr>
<tr>
<td>Adynovate</td>
<td>No</td>
<td>PEGylation</td>
<td>14.7 +/- 3.8</td>
</tr>
<tr>
<td>Nuwiq</td>
<td>Yes</td>
<td>-</td>
<td>17.1 +/- 11.2</td>
</tr>
<tr>
<td>Eloctate</td>
<td>Yes</td>
<td>Fc-fusion</td>
<td>19.7 +/- 2.3</td>
</tr>
<tr>
<td>Jivi</td>
<td>Yes</td>
<td>PEGylation</td>
<td>19</td>
</tr>
<tr>
<td>N8-GP</td>
<td>Yes (truncated)</td>
<td>PEGylation</td>
<td>19</td>
</tr>
</tbody>
</table>

- Half-life now ~14-20 hours
- Reduce FVIII infusions by ~30%
VWF-VIII Fusion

- Bypass need for VWF “protection”
- Levels of 17% after one week
- Maybe weekly prophylaxis?
- In trials
Management of Bleeding Patient on EHL

- Use standard half-life products and base off levels
- If severe bleeding and no levels 50 units/kg of rVIII
Hemophilia B (IX)

- Less common (~20%)
- Sex-linked
- ~5% of patients have inhibitors
- Prophylaxis is standard
## Hemophilia B: Standard FIX Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Half-life (hours)*</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlphaNine SD</td>
<td>18 †</td>
<td>Plasma-derived; solvent/detergent treated</td>
</tr>
<tr>
<td>BeneFIX</td>
<td>16 to 19</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Ixinity</td>
<td>24 △</td>
<td>Recombinant</td>
</tr>
<tr>
<td>Mononine</td>
<td>23 ‡</td>
<td>Plasma-derived; mAb purified</td>
</tr>
<tr>
<td>Rixubis</td>
<td>23 to 26</td>
<td>Recombinant</td>
</tr>
</tbody>
</table>
Factor IX Doses

• (Desired Factor IX concentration - current level) x weight (kg)
  – With recombinant products need "fudge" factor of 1.2

• Or level desired*kg

• Severe: 100 units/kg (120 units/kg)
# Extended Half-Life FIX Products

<table>
<thead>
<tr>
<th>FIX EHL product</th>
<th>EHL modification</th>
<th>Half-life (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprolix</td>
<td>Fc-fusion</td>
<td>82</td>
</tr>
<tr>
<td>Rebinyn</td>
<td>PEGylation</td>
<td>93</td>
</tr>
<tr>
<td>Idelvion</td>
<td>Albumin fusion</td>
<td>102</td>
</tr>
</tbody>
</table>

Can extend prophylaxis to weekly or even every other week
rFIX-FP (Idelvion)
Pharmacokinetics

Management of Bleeding Patient on EHL

- Use standard half-life products and base off levels
- If severe bleeding and no levels 100 units/kg of IX
Emicizumab

- Novel monoclonal protein
- Major breakthrough in Hemophilia A
Emicizumab

• Two major clinical trials
  – Hemophilia A with factor inhibitor
  – Hemophilia A with no factor inhibitor
Inhibitor Patients

No prophylaxis

- No prophylaxis: 23.3
- Emicizumab: 2.9
- Reduction: 87%

Bypass prophylaxis

- Bypassing prophylaxis: 15.7
- Emicizumab: 3.3
- Reduction: 79%

% without bleeds

- No prophylaxis: 6%
- Emicizumab: 63%

- Bypassing prophylaxis: 13%
- Emicizumab: 71%

N Engl J Med 2017; 377:809-818
No Inhibitors

ARM A: 1.5 mg/kg/7 day
ARM B: 3 mg/kg/14 days
ARM C: no prophylaxis

Emicizumab

- Very effective in reducing bleeds
- Safe!
  - Thrombosis seen in early trials with high dose FEIBA use
FDA Approval

• Hemophilia A with (Nov 2017) and without inhibitors (Oct 2018)

• Dosing
  – Loading dose: 3 mg/kg weekly x 4 weeks
  – Maintenance dose:
    • 1.5 mg/kg weekly
    • 3 mg/kg every other week
    • 6 mg/kg every 4 weeks
Burn Point

- aPTT and standard Factor VIII levels not valid in patients on Emicizumab!!
- Need specialized lab assay to measure factor VIII
Acute Bleeding: Inhibitors

- **rFVIIa** at dose of 90-120 mcg/kg
- Frequency should be no more than every 2 hours
- Vast majority of bleeding should be controlled with a maximum of three doses
- Use of FEIBA *should be avoided if possible*
  - Initial dose should be 50 units/kg
  - Should not exceed 100 units/kg/day
Acute Bleeding: Without Inhibitors

- Factor VIII concentrates for treatment of breakthrough bleeding.
- Standard dosing should be used
- Need special levels
Inhibiting Inhibitors

- Blocking natural anticoagulants reduces bleeding
  - TFPI
    - Antibodies
  - Antithrombin
    - siRNA
  - Activated Protein C
    - Antibodies
    - Recombinant inhibitor
Me trying to learn the Coagulation Cascade for the 827th time
Natural Anticoagulants

AT → VII + TF → IX + VIII → X + V → II → Clot

TFPI → PC + PS
Fitusiran (AT) Bleeding Events

<table>
<thead>
<tr>
<th></th>
<th>AT Lowering &lt;25%</th>
<th>AT Lowering 25-50%</th>
<th>AT Lowering 50-75%</th>
<th>AT Lowering &gt;75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients†</td>
<td>30</td>
<td>27</td>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>Cumulative Days</td>
<td>733</td>
<td>1119</td>
<td>1203</td>
<td>1128</td>
</tr>
<tr>
<td>Cumulative Bleeds</td>
<td>47</td>
<td>40</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>ABR², Mean (SEM)**</td>
<td>22 ± 5</td>
<td>15 ± 6</td>
<td>11 ± 3</td>
<td>5 ± 2</td>
</tr>
<tr>
<td>ABR, Median</td>
<td>10</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

Pasi, WFH, 2016
Exploratory Outcome of ABR Reduction

Spontaneous Joint Bleeds

At highest dose of 1.2 mg/kg, median spontaneous joint bleeds ABR reduced from 21.1 to 2.2

0.3 mg/kg
n=7
p=0.016

0.6 mg/kg
n=7
p=0.031

1.2 mg/kg
n=8
p=0.023

11BIC 2021
But....

• Thrombosis – including fatal - has been an issue in clinical trials
• Need right balance of inhibition
**Fitusiran: Thrombotic Risk and AT Level**

AT level is a predictor of thrombosis risk:

<table>
<thead>
<tr>
<th>AT Level</th>
<th>Incidence Thrombosis/100 pt-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT &lt; 10%</td>
<td>5.91</td>
</tr>
<tr>
<td>AT 10-20%</td>
<td>1.49</td>
</tr>
<tr>
<td>AT &gt; 20%</td>
<td>0</td>
</tr>
</tbody>
</table>

**Goal:** Maintain AT level above 20% to prevent thrombosis.

Will that also be an effective dose to prevent bleeds?
Phase I Trial: Safety & Mitigation Procedures

Breakthrough bleeds: Use low doses of factor and bypass agent
FVIII: 10-20 IU/kg
FIX: 20-30 IU/kg
FVIIa: 45 mcg/kg
aPCC: 30 IU/kg
Keep a diary of factor treatment
Call if continuing dosing is required
Avoid antifibrinolytics when using factor or bypass agent

Surgery: For procedure, schedule at nadir: 2 weeks after dose
Use low-dose VIII, IX, rVIIa pre, post surgery for hemostasis

Educate patients: Symptoms, risks of thrombosis
Bottom Line

• Interesting concept
• Allows for infrequent dosing
• Balance of thrombosis vs bleeding major issue
Gene Therapy

- Hemophilia ideal disease for gene therapy
  - Low levels of gene expression would provide protection
  - Easy to measure lab and clinical endpoints
  - Biology of Factor VIII and IX understood
## Hemophilia Severity

<table>
<thead>
<tr>
<th></th>
<th>Factor VIII/IX Activity</th>
<th>Spontaneous Bleeding</th>
<th>Bleeding After Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>&gt;40%</td>
<td>No</td>
<td>-</td>
</tr>
<tr>
<td>Mild</td>
<td>6-40%</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5%</td>
<td>Occasional</td>
<td>Yes</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1%</td>
<td>Frequent (Hemarthrosis)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Factor VIII: Gene Therapy

- Factor VIII is BIG! (2351 AA)
  - Too big to be fit into vectors
  - B domain is deleted
- Liver specific promoter inserted
- Recombinant adenovirus vector
- Administered IV
# Hemophilia A Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Generic/product name</th>
<th>NC no.</th>
<th>Phase</th>
<th>N</th>
<th>Dose of vector (/kg BW)</th>
<th>Expression level short term (1-6 mo)*</th>
<th>1 y (IU/dL or %)</th>
<th>&gt;2 y (IU/dL or %)</th>
<th>Duration and stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>Valoctocogene roxaparvovec (AAV5 BMN 270)</td>
<td>NCT02576795</td>
<td>1/2</td>
<td>7</td>
<td>$6 \times 10^{13}$</td>
<td>Gradual increase up to 24 wk</td>
<td>60 (median)</td>
<td>36 (median)</td>
<td>Expression declining after 1 y to 33 (mean) and 20 (median) after 3 y</td>
</tr>
<tr>
<td>BioMarin Pharmaceuticals</td>
<td>Valoctocogene roxaparvovec (AAV5 BMN 270)</td>
<td>NCT03370913</td>
<td>3</td>
<td>134</td>
<td>$6 \times 10^{13}$</td>
<td>n.a.</td>
<td>23.9 (median)</td>
<td>n.a.</td>
<td>No long-term data available</td>
</tr>
<tr>
<td>Spark Therapeutics</td>
<td>SPK-8011, AAV LK03-co-BDD-F8</td>
<td>NCT03003533</td>
<td>1/2</td>
<td>7</td>
<td>$2 \times 10^{12}$</td>
<td>16.49 (n = 5), response &lt; 5 in 2 patients</td>
<td>5.2-19.8 (n = 5)</td>
<td>n.a.</td>
<td>Two patients lost expression</td>
</tr>
<tr>
<td>Sangamo Therapeutics/Pfizer</td>
<td>Giroctocogene fitelparvovec SB-525, AAV6-co-BDD-F8 (ALTA-Study)</td>
<td>NCT03061201</td>
<td>1/2</td>
<td>5</td>
<td>$3 \times 10^{13}$</td>
<td>Increase to normal range within 5 wk</td>
<td>50.2 (median steady state)</td>
<td>n.a.</td>
<td>Follow-up too short for evaluation of durability</td>
</tr>
<tr>
<td>Bayer</td>
<td>BAY2599023 (DTX 201) AAVhu37-GET-8 study</td>
<td>NCT03588299</td>
<td>1/2</td>
<td>2</td>
<td>$2 \times 10^{13}$</td>
<td>12 and 72</td>
<td>n.a.</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

Factor VIII Example

Mean Factor VIII Activity Levels

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Viral Therapy</th>
<th>Yr. 1</th>
<th>Yr. 2</th>
<th>Yr. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>$6 \times 10^{13}$ vg/Kg</td>
<td>64 IU/dL</td>
<td>36 IU/dL</td>
<td>33 IU/dL</td>
</tr>
<tr>
<td>4</td>
<td>$4 \times 10^{13}$ vg/Kg</td>
<td>21 IU/dL</td>
<td>15 IU/dL</td>
<td></td>
</tr>
</tbody>
</table>

Factor IX

- Small molecule (607 AA)
- Factor IX Padua
  - 10x activity of wild type IX
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Generic/product name</th>
<th>NC no.</th>
<th>Phase</th>
<th>N</th>
<th>Dose of vector (/kg BW)</th>
<th>Expression level short term (1-6 mo)*</th>
<th>1 y (IU/dL or %)</th>
<th>&gt;2 y (IU/dL or %)</th>
<th>Duration and stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxalta/Takeda</td>
<td>AAV8-ccF9-Padua Bax 335</td>
<td>NCT01687608</td>
<td>1/2</td>
<td>2</td>
<td>3 x 10^{12}</td>
<td>45.3 (mean peak levels) (range 32-59) (OSA)</td>
<td>n.a.</td>
<td>20 (one patient)</td>
<td>Transient, short-term expression in 7; loss of expression in 6 out of 7</td>
</tr>
<tr>
<td>UniQure Biopharma</td>
<td>AAV5-hFIX (AMT-060)</td>
<td>NCT02396342</td>
<td>1/2</td>
<td>5</td>
<td>2 x 10^{13}</td>
<td>6.9 (mean (95% Cl, 2.6-11.3) (OSA)</td>
<td>n.a.</td>
<td>7.4 (95% Cl 4.2-10.6)</td>
<td>Stable expression over 5 y</td>
</tr>
<tr>
<td>Spark Therapeutics/Pfizer</td>
<td>Fidanacogene elapavovec SPK-9001, mutant AAV8-ccF9-Padua Factor IX-long study</td>
<td>NCT03307980</td>
<td>1/2</td>
<td>10</td>
<td>5 x 10^{11}</td>
<td>33.7 mean (SD 18.5) Range 14-81 (OSA)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Studies continued with lowered dose of FIX product in 2 patients</td>
</tr>
<tr>
<td>UniQure Biopharma</td>
<td>Etranacogene dezapavovec AAV5-hFIXco-Padua (AMT-061)</td>
<td>NCT03469291</td>
<td>2b</td>
<td>3</td>
<td>2 x 10^{13}</td>
<td>47 (mean (range 33.2-57.0) (OSA)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>No long-term data available</td>
</tr>
<tr>
<td>Freeline Therapeutics</td>
<td>FLT180a (B-AMAZE)</td>
<td>NCT03369444</td>
<td>1</td>
<td>2</td>
<td>1.5 x 10^{12}</td>
<td>16.0 (67-253) Mean (range at 26 wk)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>No long-term data available</td>
</tr>
<tr>
<td>UniQure Biopharma</td>
<td>AAV5-hFIXco-Padua (AMT-061)HOPE-B</td>
<td>NCT03569891</td>
<td>3</td>
<td>54</td>
<td>2 x 10^{13}</td>
<td>37.2 (mean 19.6 SD Range 1.07 (OSA)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>Stable expression over 8 y</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>AAV8 FIX-WT</td>
<td>NCT00979238</td>
<td>1</td>
<td>6</td>
<td>2 x 10^{12}</td>
<td>1.4-7.2 (range (OSA)</td>
<td>5.1 mean (SD 1.7)</td>
<td>n.a.</td>
<td>Transient, short-term expression</td>
</tr>
<tr>
<td>UCL/St Jude's CRH</td>
<td>DTX101, AAV1h10FIX</td>
<td>NCT02618915</td>
<td>1/2</td>
<td>3</td>
<td>5 x 10^{12}</td>
<td>12-20 (range reached within 3-8 wk)</td>
<td>Gradual decrease to baseline</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

Gene Therapy: Factor IX

Gene Therapy: Issues

• Many patients need steroids to keep factor production up
  • All trials give with infusion
  • Some need steroids > 6 months
• AAV antibodies frequent
  • May be “immunoabsorbed”
• Duration of benefit is unclear
• Carcinogenesis
Etranacogene Dezaparvovec

- FDA approved FIX gene therapy
- Can be administer in hemophilia centers
- Cost: ~ 3,500,000
Acquired Factor Inhibitors

• Rare but spectacular cause of bleeding
• Specific inhibitory antibody forms to coagulation factor
• Underlying disease
  – Autoimmune disease
  – Cancer
  – Older age
Acquired Factor Inhibitors

- Most common is factor VIII
- Presentation: sudden onset of bruising and bleeding, excessive bleeding from surgery sites
Acquired Factor VIII Inhibitors

• Dx: elevated aPTT that corrects (or near corrects) at time zero but prolongs with incubation
  – Measurement of specific factor levels
Therapy for Coagulation Inhibitors

• Two goals
  – Drive away antibodies
  – Correct coagulation defects
Drive Away Antibodies

- Steroids
  - 60 mg daily
- Cyclophosphamide
  - 100mg po daily
- Rituximab
  - 1000mg x 2 14 days apart
Correct Coagulation Defects

- Infused VIII is ineffective
- Porcine factor VIII
- Activated prothrombin complex concentrates
- rVIIa
RVIIa

• 90 ug/kg ~ q2-3 until hemostasis
  – Then every 6 for 24 hrs?
• Risk of thrombosis minimal
FIEBA

- 50 units/kg 6 hrs
- Contraindicated if patient getting emicizumab
Obizur

- Porcine Factor VIII
  - 200 units/kg load then 100 units/kg bid
- Can develop inhibitors
Emicizumab

- Increasing use in acquired inhibitors
- Started at 3mg/kg weekly
- Quickly effective
- Difficult to monitor VIII levels
Conclusions

• Lots of action in this field!
• Extended half-life products and emicizumab major impacts
• Anti-natural anticoagulant therapy
  • Promising but risky
• Gene therapy
  • Lots of trials