Non-Malignant Hematology: Changing Paradigms

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Disclosures

- Research - Baxalta, Bayer, NovoNordisk, Octapharma
- Advisory Boards - Baxalta, Bayer, Biogen, Boehringer Ingelheim, Genentech, NovoNordisk, Octapharma, Pfizer
- DSMB - NIH, Dimension, Revo, Georgetown
- Stock - Not applicable
- Employment – Not applicable
- Speakers’ Bureau – Not applicable
Topics

- Advances in Hemophilia
  - Plasma vs recombinant replacement product
  - Inhibit the inhibitor
- Gene therapy: hemophilia, thal, SS disease
- Special clinical situations for DOACS
- New antidotes to DOACs
- Landscape of atypical HUS
- Miscellaneous
# Treatment Timeline

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>First case of hemophilia in U.S.</td>
<td>1803</td>
</tr>
<tr>
<td>First whole blood transfusion</td>
<td>1840</td>
</tr>
<tr>
<td>Queen Victoria – hemophilia</td>
<td>1843</td>
</tr>
<tr>
<td>Deficiency of factor VIII, IX</td>
<td>1930s</td>
</tr>
<tr>
<td>Plasma</td>
<td>1936</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>1964</td>
</tr>
<tr>
<td>Clotting factor: VII, IX, PCC</td>
<td>1960-80s</td>
</tr>
<tr>
<td>Liver transplant: cure</td>
<td>1985</td>
</tr>
<tr>
<td>FIX, FVIII genes cloned</td>
<td>1982-84</td>
</tr>
<tr>
<td>Recombinant factor VIII, IX, VIIa</td>
<td>1992-99</td>
</tr>
<tr>
<td>Extended Half-Life VIII, IX</td>
<td>2010-15</td>
</tr>
</tbody>
</table>

Queen Victoria’s Family

Cross-segment therapies  2016-17

Gene therapy  2016-2019
Emerging Clinical Concepts

• Exciting time in clot factor management:
  – Extended half-life proteins for hemophilia

• Paradigm shift in treatment:
  1. Fewer infusions
  2. Longer protection from bleeds
  3. Improved quality of life
  4. Reduced immunogenicity
Hemophilia Clinical Trial Pipeline

**Hemophilia With Inhibitors**

- **New Recombinants**
  - BAX817 – rVIIa
  - Transgenic rhFVIIa

- **Longer-acting**
  - OBI-1 – rpFVIII
  - CB813d – rVIIa analogue
  - CSL689 – rVIIa:albumin fusion
  - rVIIa:CTP

**Hemophilia A**

- **New Recombinants**
  - simoctogog alfa – rFVIII
  - octocog alfa sucrose plasma protein-free– rFVIII
  - GreenGene F - rFVIII

- **Longer-acting**
  - rFVIII:Fc*
  - BAY94-9027 – PEGylated rFVIII
  - BAY855 – PEGylated rFVIII*
  - CSL627 – SingleChain rFVIII

**Hemophilia B**

- **New Recombinants**
  - IB1001 – rFIX
  - BAX326 – rFIX *

- **Longer-acting**
  - rFIX:Fc*
  - CSL654 – rFIX:albumin fusion

**Cross-Segment**

- **Longer-acting**
  - MC710 – pdFVIIa + pdFX
  - ACE910 – SC bispecific Ab
  - siRNA vs Antithrombin
  - r anti-TFPI

* = Approved
Primary Outcome

Proportion of Children With no Cartilage/Bone Changes on MRI in 6 Index Joints at Study Exit

- **Episodic** – 55%
- **Prophylaxis** – 93%

**Median number of joint bleeds**

- Prophylaxis vs Episodic arm:
  - 0.2 vs 4.35/y

**Prophylaxis → 83% relative risk reduction**

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EHL Dosing

**SHL:** 25-25-50 U/kg TIW rFVIII  
**EHL:** 25/65 U/kg BIW rFVIIIIFc

**SHL:** 75-100 U/kg BIW rFIX  
**EHL:** 75-100 U/kg 1/wk rFIXFc

# EHL Proteins

<table>
<thead>
<tr>
<th>Protein</th>
<th>Phase</th>
<th>Dose (IU/kg)</th>
<th>Subjects</th>
<th>ABR</th>
<th>Response</th>
<th>Inhibitor</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recombinant FVIII EHL Proteins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFVIIIFc&lt;sup&gt;a&lt;/sup&gt;</td>
<td>III</td>
<td>25-50</td>
<td>2/wk</td>
<td>N = 165</td>
<td>2.9</td>
<td>97.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>N8-GP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>III</td>
<td>50</td>
<td>q 4d</td>
<td>N = 175</td>
<td>1.3</td>
<td>95.5%</td>
<td>0.0%</td>
</tr>
<tr>
<td>BAY 94-9027&lt;sup&gt;c&lt;/sup&gt;</td>
<td>III</td>
<td>25-60</td>
<td>1-2/wk</td>
<td>N = 132</td>
<td>1.5</td>
<td>--</td>
<td>0.0%</td>
</tr>
<tr>
<td>PEG-rFVIII</td>
<td>III</td>
<td>45</td>
<td>2/wk</td>
<td>N = 101</td>
<td>1.9</td>
<td>95.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Recombinant FIX EHL Proteins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rFIXFc&lt;sup&gt;e&lt;/sup&gt;</td>
<td>III</td>
<td>50-100</td>
<td>q 7-10d</td>
<td>N = 61</td>
<td>2.0</td>
<td>97.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>rFIX-FP&lt;sup&gt;f&lt;/sup&gt;</td>
<td>III</td>
<td>50-75</td>
<td>q 7-14d</td>
<td>N = 63</td>
<td>--</td>
<td>98.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>N9-GP&lt;sup&gt;g&lt;/sup&gt;</td>
<td>III</td>
<td>40</td>
<td>q wk</td>
<td>N = 29</td>
<td>1.0</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

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The mean $t_{1/2}$ of N9-GP was 93 hours which was approximately 5 times longer compared with the patients' previous FIX product ($P < .001$).
EHLs: Clinical Trials Update

- Phase 3 Clinical Trials
- Safe, well tolerated
- Improved t½, recovery; delayed clearance
- No inhibitor development
- No allergic reactions
- No thrombosis
- Efficacy comparable to rFVIII, rFIX
- Safety comparable to rFVIII, rFIX
Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET)

- Study of inhibitory antibodies
- Screening
  - Age < 6y
  - Plasma FVIII activity < 1%
  - No previous FVIII concentrate treatment
  - Blood component exposure < 5 times
- Randomized for FVIII replacement

Plasma derived (pdFVIII, n = 125)  Recombinant (rFVIII, n = 126)

SIPPET Results

High titer (peak > 5 BU/ml)
• pdFVIII: 18.6%
• rFVIII: 28.4%
• HR: 1.69

Antibody Analog of Factor VIII (FVIII): Emicizumab

Emicizumab Impact on ABR

No bleeding
- 73% of patients with FVIII inhibitors
- 71% of patients without factor VIII inhibitors

“Inhibit-the-Inhibitor” Strategies

**“Intrinsic” pathway**
- XII → XIIa
- PreK → XII
- XIa → Ca
- Ca → Xa
- Xa → Ca
- Ca → Thrombin
- Thrombin → Fibrinogen
- Fibrinogen → Fibrin

**“Extrinsic” pathway**
- VII → VIIa
- TF → PL → Ca
- Ca → Xa
- Xa → Ca
- Ca → Thrombin
- Thrombin → Fibrinogen
- Fibrinogen → Fibrin

**Cross-talk**
- XII → XIa → Ca
- Ca → Xa
- Xa → Ca
- Ca → Thrombin
- Thrombin → Fibrinogen
- Fibrinogen → Fibrin

**Feedback**
- Thrombin → Antithrombin
- Antithrombin → TFPI

**Initiation**
- Thrombin

**Amplification**
- Fibrinogen

**Propagation**
- Fibrin
Safety and PK of Anti-TFPI Antibody Concizumab

- Dose-dependent procoagulant effect
  - Increased levels of D-dimers and drugs
  - Not associated with coagulation factor inhibitors
  - Good solubility and stability
  - Long plasma T½
  - High selectivity and specificity

- Others in Phase 1
  - BAY 1093884
  - PF 6741086

N = 3/group

Phase 1 Antithrombin RNAi Results
ALN-AT3/Fitusiran

Bleeding By AT Quartile
ALN-AT3/Fitusiran

<table>
<thead>
<tr>
<th>AT Lowering</th>
<th>Patients</th>
<th>Cumulative Days</th>
<th>Cumulative Bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>24</td>
<td>602</td>
<td>43</td>
</tr>
<tr>
<td>25-50%</td>
<td>21</td>
<td>838</td>
<td>34</td>
</tr>
<tr>
<td>50-75%</td>
<td>18</td>
<td>862</td>
<td>35</td>
</tr>
<tr>
<td>&gt;75%</td>
<td>9</td>
<td>304</td>
<td>3</td>
</tr>
</tbody>
</table>

SPK-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B Achieves Sustained Mean Factor IX Activity Levels of >30%

Transgene-derived FIX activity among all subjects

Mean steady-state FIX activity was 28.3 ± 10.0% of normal (12-52 weeks follow up)
No vector or procedure related unexpected adverse events, 1 subject had grade I transaminase toxicity
No patients developed FIX alloinhibitory antibodies (inhibitors)

- Naturally occurring mutation with approximately 8X greater specific activity
- Safety:
  - Enhanced factor X activation (Samelson-Jones BJ et al, Abstract 1384)
SPK-9001: Adeno-Associated Virus Mediated Gene Transfer for Hemophilia B Achieves Sustained Mean Factor IX Activity Levels of >30%

Reduction in annualized bleeding rate and factor consumption

Annualized Bleeding Rate

52 Weeks Before Vector  |  After Vector
---|---
4 | 0
1 | 0
12 | 0
10 | 0
2 | 2
49 | 0

Factor Infusions

52 Weeks Before Vector  |  After Vector
---|---
On Demand Dose  |  Prophylaxis Dose

99% reduction in factor, savings of >1.1 million IU or >$2.1 million USD
## Factor VIII Levels of High Dose Patients* by Visit (N=7)

<table>
<thead>
<tr>
<th>BIOMARiN</th>
<th>Week**</th>
<th>n***</th>
<th>Median Factor VIII Level**** (%)</th>
<th>Mean Factor VIII Level**** (%)</th>
<th>Range (high, low)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>7</td>
<td>97</td>
<td>118</td>
<td>(12, 254)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>7</td>
<td>101</td>
<td>130</td>
<td>(16, 227)</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>7</td>
<td>122</td>
<td>124</td>
<td>(15, 257)</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>6</td>
<td>99</td>
<td>122</td>
<td>(26, 316)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>7</td>
<td>99</td>
<td>115</td>
<td>(31, 273)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>6</td>
<td>115</td>
<td>127</td>
<td>(17, 264)</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>2</td>
<td>119</td>
<td>119</td>
<td>(105, 133)</td>
</tr>
</tbody>
</table>

**Patients have maintained FVIII levels >200%**

January 9th 2017
Update from the HGB-205 Phase 1/2 Clinical Study of LentiGlobin Gene Therapy: Sustained Clinical Benefit in Severe Hemoglobinopathies

STUDY DESIGN

Autologous CD34+ cells transduced with lentiviral vector, encoding human Beta globin point mutation (AT87Q) to confer HGB AT$^{(T87Q)}$
Update from the HGB-205 Phase 1/2 Clinical Study of LentiGlobin Gene Therapy: Sustained Clinical Benefit in Severe Hemoglobinopathies

**HbA\textsuperscript{T87Q} Production**

- First subject with severe sickle cell disease treated with gene therapy continues free of clinical symptoms 21 months after receiving LentiGlobin Drug Product
  - Consistent production of therapeutic hemoglobin HbA\textsuperscript{T87Q}
  - No further evidence of hemolysis
  - No hospitalizations, VOC, or other clinical SCD symptoms since treatment, despite weaning off transfusions
- Ongoing transfusion independence and sustained production of HbA\textsuperscript{T87Q} in patients with transfusion-dependent β-thalassemia
  - Stable total hemoglobin levels >10 g/dL in patients with β\textsuperscript{0}/β\textsuperscript{E} genotypes
  - Patient 1202 no longer requires iron chelation therapy
- Safety profile of LentiGlobin Drug Product appears consistent with autologous transplantation, with no gene-therapy related adverse events to date and with continued polyclonal reconstitution
- Study HGB-205 demonstrates continued promise of gene therapy with LentiGlobin BB305 in both severe SCD and TDT

**Freedom from pRBC Transfusion**

- Patient 1202 has discontinued iron chelation and transitioned to therapeutic phlebotomy

- **Total Hb**
  - 1201: 33.1
  - 1202: 29.9
  - 1203: 11.6
  - 1206: 11.5

*Hemoglobin (g/dL) at most recent study visit*
Data are limited for use of IVC filters in CA pts

Retrospective study of 1272 CA pts with prior PE from MSKCC

- Lung (N=246), colorectal (N=139), gynecologic (N=130), and breast (N=103)
- 25% (N=317) had IVCF placed and compared to the 955 pts w/o IVCF
- The indications for IVCF: AC contraindicated (39%), pre-operative (16%), AC failure (16%), poor cardiopulmonary reserve (6%) or indication unclear (23%)
Coombs C et al.

Composite 12-mo rate of recurrent VTE w/IVCF=14% vs 8%, (p= 0.016)

Adjusting for whether pts on AC at time of PE, VTE w/IVCF still remained statistically significant with p= 0.014.

After adjusting for AC, the risk of recurrent PE was similar between the IVCF cohort (5%) and non-IVCF (4%), (p= 0.43), but the risk of DVT was significantly higher in the IVCF group, 9% versus 5% (p= 0.014)

**Median OS w/IVCF=7.4 vs 13.5 mos in non-IVCF, p= <0.001**

Median time from IVCF placement to death = 3.6 mos (range 0.07-88.4 months) with 14% placed within 1 month of death
In-hospital all-cause case fatality rate among patients with solid malignant tumors according to age. IVCF = inferior vena cava filter. Case fatality rate among those who did not receive a filter (No IVCF) increased linearly with age ($r = 0.9575$, slope = 1.22 deaths/100 patients/10 years of age, $P = .0007$). Case fatality rate with IVCF was not linearly related to age.

Only those who were older than 30 years of age had a lower in-hospital all-cause case fatality rate with filters.

http://dx.doi.org/10.1016/j.amjmed.2013.03.030  The American Journal of Medicine, Volume 126, Issue 9, 2013, 819–824
SITES OF ACTION

Steps in Coagulation | Pathway | Drugs
--- | --- | ---
Initiation | TF/VIIa | Rivaroxaban
Propagation | Xa | Apixaban, Edoxaban, Betrixaban
Fibrin formation | IIa | Dabigatran

Hankey GJ and Eikelboom JW. Circulation 2011;123:1436-1450
## Clinical Comparisons of the Novel Oral Anti-Xa Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tmax</strong></td>
<td>1.5 - 3 hrs</td>
<td>2 - 4 hrs</td>
<td>1 - 3 hrs</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td><strong>Half life</strong></td>
<td>12 - 14 hrs</td>
<td>9 - 13 hrs</td>
<td>8 - 15hrs</td>
<td>9-11 hrs</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80%</td>
<td>66 %</td>
<td>ca. 25 %</td>
<td>35%</td>
</tr>
<tr>
<td><strong>FDA approval</strong></td>
<td>• A. fib</td>
<td>• A. fib</td>
<td>• A. fib</td>
<td>• A. fib</td>
</tr>
<tr>
<td></td>
<td>• VTE</td>
<td>• VTE</td>
<td>• Ortopedic VTE prevention/ THR/TKR</td>
<td>• VTE prophy and TX;</td>
</tr>
<tr>
<td></td>
<td>treatment</td>
<td>prevention</td>
<td>treatment</td>
<td>60 mg qd</td>
</tr>
<tr>
<td></td>
<td>Secondary VTE prevention</td>
<td>VTE prevention</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In clinical development: Betrixaban (not FDA approved)
DOAC in VTE Treatment

Control Group
- LMWH/UFH
- Vitamin K antagonist (INR 2.0 to 3.0)

RECOVER I+ II
- LMWH/UFH
- Dabigatran 150 mg BID x 6 mos

EINSTEIN DVT + PE
- Rivaroxaban 15 mg BID x 3 wk then 20 mg OD x 3, 6, or 12 mos

AMPLIFY
- Apixaban 10 mg BID x 7 d then 5 mg BID x 6 mos

Hokusai
- LMWH/UFH
- Edoxaban 60 mg OD x 3, 6, or 12 mos

5 – 7 days 1 month 6 months 12 months
DOAC in VTE Treatment

Non-inferior to VKA in preventing recurrent VTE

## DOAC in Patients with Cancer

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Cancer/Total n/N (%)</th>
<th>Recurrent VTE, %</th>
<th>Major and CRB,%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DOAC</td>
<td>VKA</td>
</tr>
<tr>
<td>Dabigatran&lt;sup&gt;1&lt;/sup&gt;</td>
<td>335/4772 (4.8%)</td>
<td>5.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;2&lt;/sup&gt;</td>
<td>207/3449 (6.0%)</td>
<td>3.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Rivaroxaban&lt;sup&gt;3&lt;/sup&gt;</td>
<td>223/4832 (4.6%)</td>
<td>1.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Apixaban&lt;sup&gt;4&lt;/sup&gt;</td>
<td>143/5395 (2.7%)</td>
<td>3.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Edoxaban&lt;sup&gt;5&lt;/sup&gt;</td>
<td>771/8240 (9.4%)</td>
<td>3.7</td>
<td>7.1</td>
</tr>
</tbody>
</table>

CRB, clinically relevant bleeding; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Recurrent VTE in DOAC

- post-hoc subgroup analysis of cancer patients in EINSTEIN-DVT and EINSTEIN-PE trials
- enrolled 462 patients with active cancer at baseline
- risk of recurrent VTE differed wrt cancer status

<table>
<thead>
<tr>
<th>Cancer Status</th>
<th>N</th>
<th>Recurrent VTE, %</th>
<th>Major and CRB, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban</td>
<td>VKA</td>
</tr>
<tr>
<td>No cancer</td>
<td>7157</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>History of cancer</td>
<td>469</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Cancer at baseline</td>
<td>462</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Cancer during study</td>
<td>193</td>
<td>10%</td>
<td>12%</td>
</tr>
</tbody>
</table>

- no statistical difference between rivaroxaban and VKA

Limitations of DOAC in Cancer Patients

- sparse details regarding cancer and prognostic factors
- “healthier” cancer patients compared with LMWH studies
- no comparison against long-term LMWH for treatment
- unreliable administration and absorption in patients with GI toxicity and mucosal erosion
- higher risk of GI bleed for dabigatran and rivaroxaban
- therapeutic range not established
- drug interactions difficult to predict, especially with multi-agent regimens
DOAC Drug Interactions

• inhibitors and inducers of P-glycoprotein +/- CYP3A4:

- antifungals
  - ritonavir
  - amiodarone
  - verapamil
  - clarithromycin
  - quinidine
  - tamoxifen
  - TKIs
  - cyclosporin
  - tacrolimus

- Inducers
  - rifampicin
  - phenytoin
  - carbamazepine
  - phenobarbitone
  - dexamethasone
  - doxorubicin
  - vinblastine
  - St. John’s wort
CLOT Trial:
Results: Symptomatic Recurrent VTE

- **Probability of Recurrent VTE, %**
- Risk reduction = 52%
- HR 0.48 (95% CI 0.30, 0.77)
- Log-rank p = 0.002

- **Days Post Randomization**
- **Dalteparin, 9%**
- **VKA, 17%**

DALTECAN
Study Design

- Phase IV, 52 week, multicenter, single arm, open-label worldwide study.
  - Approximately 50 sites in the US, Canada, and Europe.

SUBJECTS:
338 adult subjects
- Active cancer
- New VTE*

Total daily dose not to exceed 18,000 IU

Dalteparin 200 IU/kg

Month 1

First 6 Month Cohort

Month 6

Second 6 Month Cohort

Month 12

*Objectively confirmed by diagnostic testing.
DALTECAN
Conclusions

• Extending dalteparin therapy in patients with VTE and cancer beyond 6 months is not associated with an increase in major bleeding compared to the initial period of therapy.
  – The highest rate of major bleeding was in the first month (5.6%).
  – The overall incidence of major bleeding per patient-month was similar between months 2-6 as compared to months 7-12 (1.1% vs. 0.7% per month).

• VTE recurrence rates were highest in the first 6 months (8.7%) but despite treatment with LMWH, the risk of VTE recurrence is still clinically important in months 7-12 (4.1%).

• Patient adherence to a 12 month regimen in patients surviving and remaining in study, was high.
## Specific DOAC Reversal Agents: Mechanisms

<table>
<thead>
<tr>
<th>NOAC reversal agent</th>
<th>Target</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Dabigatran</td>
<td>Idarucizumab binds Dabigatran with high affinity</td>
</tr>
<tr>
<td>Andexanet alpha</td>
<td>Factor Xa inhibitors</td>
<td></td>
</tr>
</tbody>
</table>

### Mechanisms

**Phospholipid membrane**

- **Apixaban**
- **Argatroban**
- **Edoxaban**
- **Dabigatran**
- **Rivaroxaban**
- **UFH**
- **LMWH**
- **Fondaparinux**

**Ciraparantag (PER977)**

Computer-aided energy minimization modeling predicts 8 non-covalent binding sites on ciraparantag for NOACs or heparins.
Management of DOAC Treated Patients Requiring Invasive Intervention

Is normal hemostasis required & does intervention have to be performed <24 hours?

YES

Measure anticoagulant activity:
- Dabigatran - dilute thrombin time or ecarin clotting time (aPTT a reasonable alternative*)
- FXa Inhibitors - chromogenic anti-FXa assay (PT an option if anti-FXa assay not available*)

Coagulation Test Abnormal?

YES

Reversal Agents:
- Dabigatran – idarucizumab (ciraparantag if approved)
- FXa inhibitors – PCC (andexanet or ciraparantag if approved)

NO

Intervention can be performed:
- 24–48 hrs after last dose of NOAC depending on renal function and bleeding risk of surgery
- If on dabigatran and moderate-severe renal dysfunction wait ≥48–96 hours depending on severity of renal dysfunction and risk of surgery

NO

No reversal agent needed
Rituximab naïve group: timing of first infusion and outcome

<table>
<thead>
<tr>
<th></th>
<th>≤3 days from admission (n=52)</th>
<th>&gt;3 days from admission (n=30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median No. of PEX to CR (range)</td>
<td>16 (4-36)</td>
<td>24 (6-40)</td>
<td>0.03</td>
</tr>
<tr>
<td>Median Length of admission (range)</td>
<td>16 (4-86)</td>
<td>23 (7-52)</td>
<td>0.01</td>
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<tr>
<td>Median Time to CR from admission (range)</td>
<td>12 (4-52)</td>
<td>20 (4-42)</td>
<td>&lt;0.001</td>
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<tr>
<td>Median Time to CR from first infusion (range)</td>
<td>10 (2-50)</td>
<td>9 (0-30)</td>
<td>0.67</td>
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</tbody>
</table>

Westwood et al JTH 2013
BAX 930:
First Recombinant human ADAMTS13

- BAX 930 is a fully glycosylated, 176 kDa recombinant human ADAMTS13 protein (rADAMTS13)
- Produced in a Chinese Hamster Ovary (CHO) cell line in a plasma protein-free milieu
- Undergoes two virus inactivation steps (S/D, Nanofiltration)
- Lyophilized product for reconstitution in 5 ml diluent
- Activity measured using a fluorescence resonance energy transfer substrate (FRETS) composed of 73 amino acids from the A2 domain of von Willebrand factor (VWF)
VWF Multimer Patterns: 40 U/kg Dose Cohort

- **Large & Ultra-large Multimers**
- **Intermediate Multimers**

**Graph Details:**
- **Y-axis (Mean Concentration %):** 28 to 48
- **X-axis (Time (h)):** 0 to 300

**Legend:**
- Ultralarge
- Large
- Intermediate
- Small

**Image Notes:**
- The graph illustrates the concentration patterns of VWF multimers over time following a 40 U/kg dose. The concentration peaks and troughs are marked for Large & Ultra-large multimers and Intermediate multimers.
N-acetylcysteine (NAC)

TTP Symptoms due to UL-VWF - can VWF multimers be reduced by other means?

NAC - diminishes VWF multimer size & platelet agglutination ex vivo
Chen et al JCI 2011

NAC in TTP treatment
Li et al Transfusion 2013
Targeting VWF appears safe (no overt bleeding)
Does not treat disease (autoAb, ADAMTS13)
As an adjunct to PEX, steroids, rituximab – aid recovery???
Nanobodies are antibody-derived therapeutic proteins that contain the unique structural and functional properties of naturally-occurring heavy-chain antibodies.
Titan trial: Phase II

No. at Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
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<tbody>
<tr>
<td>Caplacizumab, no PE before randomization</td>
<td>34</td>
</tr>
<tr>
<td>Placebo, no PE before randomization</td>
<td>35</td>
</tr>
<tr>
<td>Caplacizumab, PE before randomization</td>
<td>2</td>
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<tr>
<td>Placebo, PE before randomization</td>
<td>4</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Exacerbation</th>
<th>Relapse</th>
<th>Death</th>
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<tbody>
<tr>
<td>Caplacizumab</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Peyvandi et al NEJM 2016