Non-Malignant Hematology: What have we learned this year?

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Disclosures

• Research- Takeda, Genentech, Bayer, NovoNordisk, Octapharma, Sangamo
• Advisory Boards-Baxalta, Bayer, Biogen, Biomarin, Genentech, NovoNordisk, Octapharma, Pfizer, Sangamo, Rigel, Novartis
• DSMB- NIH, Dimension, Octapharma, Revo, Georgetown
• Stock- Not applicable
• Employment – Not applicable
• Speakers’ Bureau – Not applicable
Topics

• Advances in ITP
• Advances in Sickle Cell disease
• Target specific oral anticoagulation
• New antidotes to direct oral acting anticoagulants (DOACs)
• DOACS in cancer and beyond
• COVID and coagulation
Algorithm for the selection of second-line therapy in adults with ITP
American Society of Hematology 2019 Guidelines

[Diagram showing the algorithm for the selection of second-line therapy in adults with ITP]

Neunert Blood Advances (volume 3 issue 23 pages 3829) 2019
ITP PATHOPHYSIOLOGY:
IMPAIRED IMMUNE REGULATION

• Rapid platelet destruction

• Antibodies to platelet membrane antigens
  – GP IIb/IIIa
  – GP Ib/IX

• Suppression of thrombopoiesis

• Antibodies to megakaryocyte antigens

• Requires an intact RE system

GP= glycoprotein; RE= reticuloendothelial
Multicenter Study: Response to High-Dose Dexamethasone

- At 15 mos of follow-up, 5 relapses each among subjects who achieved CR or PR/MR

Splenectomy: Long Term Outcome

- Early response rate ~80%
- Responses usually rapid
- 15% relapse rate in first year, more later
- Laparoscopic splenectomy less morbid
- Predictors of response controversial
- Immunize with Pneumococcal, Hib, Meningococcal vaccine

Rituximab response in chronic ITP

CR100=48.1%; CR150=31.8%

OR30=67.7%; OR50= 60.4%

Figure 6. Forest plot of CR100 rate after Rituximab treatment in patients with immune thrombocytopenia.

Figure 4. Forest plot of OR30 rate after Rituximab treatment in patients with immune thrombocytopenia.

Avtrombopag—the new TPO-mimetic 2019

Phase 3 study—median platelet counts

Pathophysiologic Process

↑ Platelet Destruction

Macrophage Containing One Platelet (white arrow) and Engulfing Another (black arrow)

Overall Response (OR) in chronic ITP

- Overall Response defined as \( \geq 1 \) platelet count \( \geq 50,000/\mu L \) in the first 12 weeks of fostamatinib treatment unrelated to rescue therapy.
- Overall Response occurred in 64 of 146 (44%) patients in the fostamatinib studies.

36-month Follow-up Shows Continued Response

Overall responders: patients who had ≥1 platelet count ≥50,000/µL in the first 12 weeks of Fostamatinib treatment unrelated to rescue therapy

Other Patients: Patients may have experienced clinical benefit including
- platelet counts ≥50,000/µL after the initial 12-week period
- platelet counts ≥30,000/µL
- decreases in bleeding or rescue.
This group also includes patients who did not respond.

*Data cutoff March 8, 2018 (FEP).
Shaded area includes data points with <10 patients.

Platelet Response at Anytime in Earlier Lines of Treatment

More patients responded to fostamatinib as 2nd line therapy

*A platelet response was defined as achieving ≥1 platelet count of ≥50,000/µL (without rescue therapy) at any visit.
†1st line: any combination of steroids, IVIg, and/or anti-D.
ASH 2019 Abstract.
Adult patients with primary or secondary wAIHA, documented by IgG positive DAT; failed ≥1 prior treatment for wAIHA

Efficacy endpoint: achieving Hgb >10 g/dL with an increase of ≥2 g/dL from baseline by Week 24 without rescue therapy or RBC transfusion

Rogers KA et al. ASH 2019
Evolving ITP/AIHA therapies of the future

ABS 897: Rozanolixizumab, an Anti-FcRn Antibody: Final Results from a Phase II, Multiple-Dose Study in Patients with Primary Immune Thrombocytopenia  Robak T et al.  ASH 2019

- Rozanolixizumab: targets the human neonatal Fc receptor (FcRn). By blocking IgG recycling, this SC monoclonal antibody reduces pathogenic autoantibody levels.

Table 3. Mean platelet count (PPS) and mean observed IgG concentration (PD-PPS) on Day 8, after one dose of rozanolixizumab

<table>
<thead>
<tr>
<th></th>
<th>Rozanolixizumab doses</th>
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<tbody>
<tr>
<td></td>
<td>20 mg/kg N=12</td>
<td>15 mg/kg N=12</td>
<td>10 mg/kg N=11</td>
<td>7 mg/kg N=15</td>
<td>4 mg/kg N=14</td>
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<tr>
<td>Platelet count (x10^11/L), mean (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Baseline+</td>
<td>18.0 (4–37)</td>
<td>1.2 (6–38)</td>
<td>18.5 (6–53)</td>
<td>13.7 (5–24)</td>
<td>17.7 (5–36)</td>
</tr>
<tr>
<td>Day 8</td>
<td>144.5 (9–548) *</td>
<td>17.8 (8–486)</td>
<td>40.9 (3–166)</td>
<td>21.0 (6–57)</td>
<td>27.1 (3–105)</td>
</tr>
<tr>
<td>Observed IgG concentration (g/L), mean (range)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Baseline</td>
<td>9.9 (7.3–15.8)</td>
<td>10.2 (5.8–16.0)</td>
<td>11.3 (7.2–22.5)</td>
<td>11.1 (6.7–14.7)</td>
<td>9.6 (6.2–13.4)</td>
</tr>
<tr>
<td>Day 8</td>
<td>3.9 (2.7–6.2)</td>
<td>5.1 (2.0–10.2)</td>
<td>6.2 (3.7–16.6)</td>
<td>8.2 (4.9–11.1)</td>
<td>7.1 (4.5–10.5)</td>
</tr>
</tbody>
</table>

*In the 20 mg/kg dose cohort 12 patients had baseline values, which reduced to 11 by Day 8; †Central laboratory measurements
Evolving ITP/AIHA therapies of the future

ABS 898: Inhibition of the Classical Pathway of Complement with Sutimlimab in Chronic Immune Thrombocytopenic Purpura Patients without Adequate Response to Two or More Prior Therapies  
Broome CA et al. 
ASH 2019

Figure. Mean Platelet Counts (x 10^9/L) Over Time in Patients Receiving Sutimlimab

- 7 refractory pts: unresponsive to >2 tx modes
- Platelets >50K in <24 hrs and sustained in 4 (57%); to 20-50K in another.
- Washout resulted in recurrent ↓ plts, which immediately recovered with re-tx.
- ITP is heterogeneous

(a) The value at Baseline is the average of all platelet counts during screening period including Day 0 pre-dose in Part A.
(b) The value at Part B Baseline is the average of all platelet counts during screening period in Part B.
ABS 3518: Fostamatinib, a Spleen Tyrosine Kinase (SYK) Inhibitor, for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia (wAIHA): Final Results of the Phase 2, Multicenter, Open-Label Study

Adult patients with primary or secondary wAIHA, documented by IgG positive DAT; failed ≥1 prior treatment for wAIHA

Efficacy endpoint: achieving Hgb >10 g/dL with an increase of ≥2 g/dL from baseline by Week 24 without rescue therapy or RBC transfusion

Rogers KA et al. ASH 2019
Pathophysiology of Sickle Cell disease

- Genetics: HOMOZYGOSITY for sickle cell HbS gene missense mutation (Glu6Val) in the β-globulin gene

[Diagram showing the pathophysiology of sickle cell disease]
Rationale:

Sickle cells have LOWER redox ratio (NADH: NAD\(^+\) +NADH) and thus increased oxidative stress

L-glutamine is an essential amino acid required to synthesize NAD\(^+\)

Uptake of L-glutamine is HIGHER in sickled cells $\rightarrow$ $\uparrow$ NADH and $\downarrow$ Oxidative stress; decreased sickling

Supplementation of L-glutamine shown to increase intracellular NAD\(^+\)

Hypothesis: higher L-glutamine consumption by sickled cells may be facilitated by PO L-glutamine
Results

• Primary End Point: Pain Crises over 1 yr
  median: L-glutamine 3.0 vs Placebo group 4.0 (P = 0.005); 25% reduction

• Secondary endpoint: Hospitalizations
  - median: L-glutamine 2.0 vs Placebo group 3.0 (P = 0.005); 33% reduction

• No change in H/H or hemolytic markers

• 2 Cardiac deaths in L-glutamine cohort

![Graph A: Time to First Sickle Cell-Related Pain Crisis](image1)

- 84 days vs Placebo group 54 (hazard ratio, 0.69; P = 0.02)

![Graph B: Time to Second Sickle Cell-Related Pain Crisis](image2)

- L-glutamine 212 days vs Placebo 133d (hazard ratio, 0.68; P = 0.03)
Rationale:

• Deoxygenated sickle cell hemoglobin POLYMERIZATION drives pathophysiology

• Direct inhibition of HgS polymerization has potential to favorably modify disease outcomes

• Voxelotor is a HgS polymerization inhibitor that reversibly binds to hemoglobin to stabilize the Oxygenated Hemoglobin state

• Hypothesis: voxelotor can improve markers of hemolysis (HgB, bilirubin, LDH, reticulocyte)
Voxelotor mediated significant increases in Hgb levels in a dose response manner

- No significant differences in absolute retic counts or LDH

- Secondary endpoint: Annualized Rate of Vaso-occlusive Crisis:
  - ITT: Voxelator 1500mg 2.7 vs Voxelator 900mg 2.7 vs Placebo 3.1

- The incidence of vaso-occlusive crisis DID NOT DIFFER SIGNIFICANTLY
Rationale:

• Upregulation of P-SELECTIN on endothelial cells/platelets involved in Vaso-occlusion

• Crizanlizumab is a humanized monoclonal antibody that binds P-selectin and blocks interaction with P selectin glycoprotein ligand 1

• Hypothesis: Crizanlizumab can decrease rate of sickle cell crisis at 1 year
Crizanlizumab reduced number of pain crises in SCD

Crizanlizumab 5.0mg/kg 1.63 vs Crizanlizumab 2.5mg/kg 2.01 vs Placebo 2.98

Crizanlizumab 5.0mg/kg vs Placebo (P<0.001)

Regardless of concurrent hydroxyurea use subgroup analysis
Regardless of prior crises (2-4, 5-10) subgroup analysis

Did not improve markers of hemolysis or reduce rate of hospitalization

<table>
<thead>
<tr>
<th>Drug</th>
<th>Crisis Reduction</th>
<th>Hemolysis Marker Reduction</th>
<th>Prolong Time to Crisis</th>
<th>Cost</th>
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<tbody>
<tr>
<td>L-Glutamine</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>$65/yr</td>
</tr>
<tr>
<td>Voxelotor (HbB polym inh)</td>
<td>No</td>
<td>Yes</td>
<td>n/a</td>
<td>$120,000/yr</td>
</tr>
<tr>
<td>Crizanlizumab (P-selectin)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>$1,2000,000/yr</td>
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</tbody>
</table>
**MARINER Trial**

**Primary Efficacy Endpoint**

**A Symptomatic VTE or VTE-Related Death**

Hazard ratio, 0.76 (95% CI, 0.52–1.09)

P=0.14

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**No. at Risk**

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>6012</td>
<td>5989</td>
<td>5970</td>
<td>5959</td>
<td>5943</td>
<td>5922</td>
<td>5910</td>
<td>5902</td>
<td>5890</td>
<td>0</td>
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<tr>
<td>Rivaroxaban</td>
<td>6007</td>
<td>5989</td>
<td>5972</td>
<td>5962</td>
<td>5948</td>
<td>5934</td>
<td>5927</td>
<td>5919</td>
<td>5913</td>
<td>0</td>
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</table>

MARINER Trial
Symptomatic VTE

MARINER Trial
Major Bleeding Complications

Cancer-associated Thrombosis (CAT)

Scope of the Problem

12.6% rate of VTE 3-12 mos from diagnosis in US ambulatory patients with bladder, colorectal, lung, ovary, pancreas, or gastric cancers

6-month cumulative incidence of arterial thromboembolism 4.7% (2% MI, 3% stroke) with cancer v 2.2% in controls (HR: 2.2)
What evidence do we have for use of DOACs in primary prevention of VTE in CA patients?
AVERT: Results

![Graph showing the percentage of patients alive without venous thromboembolism over days for Apixaban and Placebo groups.]

- **Apixaban**: 95.8%
- **Placebo**: 89.8%

No. at Risk:
- Apixaban: 288, 276, 265, 256, 249, 244, 244, 229
- Placebo: 275, 268, 259, 244, 237, 228, 215

NNT = 17

## AVERT: Results

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=288)</th>
<th>Placebo (n=275)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td>4.2%</td>
<td>10.2%</td>
<td>0.41</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PE</td>
<td>2.4%</td>
<td>4.4%</td>
<td>(0.26-0.43)</td>
<td></td>
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<tr>
<td></td>
<td>1.7%</td>
<td>5.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Death from any cause</td>
<td>12.2%</td>
<td>9.8%</td>
<td>1.29</td>
<td>(0.98-1.71)</td>
</tr>
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</table>

NNT=17

# AVERT: Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=288)</th>
<th>Placebo (n=275)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Major bleeding</strong></td>
<td>3.5%</td>
<td>1.8%</td>
<td>2.0 (1.01-2.395)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Secondary CRNM bleeding</strong></td>
<td>7.3%</td>
<td>5.5%</td>
<td>1.28 (0.89-1.84)</td>
<td></td>
</tr>
</tbody>
</table>

On-treatment NNH = 100

Carrier et al, *NEJM* 2019
**CASSINI Primary Outcome: All Randomized Patients**

**Up to Day 180 (primary)**

- Placebo: 8.79%
- Rivaroxaban: 5.95%

HR, 0.66; 95% CI, 0.40-1.09; \( P = 0.101 \)

NNT=35

Khorana et al, LBA-1, *ASH 2018; NEJM 2019*

**On-treatment**

- Placebo: 6.41%
- Rivaroxaban: 2.62%

HR, 0.40; 95% CI, 0.20-0.80; \( P = 0.007 \)

NNT=26
Sites of major bleeding included gastrointestinal (n=8), intraocular (n=2), and intracranial (n=2). Fatal bleed (n=1, rivaroxaban arm).

**NNH=101 (MB), 135 (CRNMB)**
What evidence do we have for use of DOACs in secondary prevention of recurrent VTE in CA patients?
Major bleeding is increased in cancer VTE patients: Hokusai VTE Cancer Study

- Excess in upper gastrointestinal bleeding (in patients with gastrointestinal cancers) with edoxaban
- 6 deaths due to VTE in edoxaban group; 4 with dalteparin
- 2 deaths related to bleeding, both with dalteparin

(6.9% vs. 4.0%, P=0.04)

No. at Risk
Edoxaban  522  484  447  426  404  375  358  343  323  308  282  248  168
Dalteparin 524  497  466  436  409  390  378  356  346  335  298  262  183

1. LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over VKA

2. There is an increase in major bleeding risk with NOACs, particularly in GI and potentially GU cancer. Caution with NOACs also with high risk for mucosal bleeding. DDI should be checked prior. (Evidence high; Strength strong).

3. AC with LMWH, NOACs, or VKAs > 6 months should be offered to selected patients with active cancer, such as metastatic disease or chemotherapy.

AC > 6 months needs to be assessed intermittently for favorable risk-benefit profile (informal consensus; Evidence low; Strength weak to moderate).

[Caveat: Await RCT with Apixaban]
Incidence of Thrombotic Manifestations of COVID-19

- Risk factors for thrombosis:
  - Advanced age
  - Sex (male)
  - Obesity
  - Active cancer

<table>
<thead>
<tr>
<th>ICU or ward setting (n)</th>
<th>Thromboprophylaxis</th>
<th>Number of events, n (%)</th>
<th>Type of event (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese ICU (81)¹</td>
<td>None</td>
<td>20 (25)</td>
<td>DVT (20)</td>
</tr>
<tr>
<td>French ICU (26)²</td>
<td>LMWH or UFH</td>
<td>18 (69)</td>
<td>DVT (18)</td>
</tr>
<tr>
<td>Dutch ICU (184)³</td>
<td>LMWH</td>
<td>31 (17)</td>
<td>PE (25), DVT (3), stroke (3)</td>
</tr>
<tr>
<td>French ICU (150)⁴</td>
<td>LMWH or UFH</td>
<td>64 (43)</td>
<td>PE (25), DVT (3), stroke (2), limb ischemia (1), CRRT filter (28/29), ECMO (2/12)</td>
</tr>
<tr>
<td>Dutch ICU (74)⁵</td>
<td>LMWH</td>
<td>29 (39)</td>
<td>PE (9), DVT (20)</td>
</tr>
<tr>
<td>French ICU (107)⁶</td>
<td>LMWH or UFH</td>
<td>22 (21)</td>
<td>PE (22)¹</td>
</tr>
<tr>
<td>Dutch ward (124)⁵</td>
<td>LMWH</td>
<td>4 (3.2)</td>
<td>PE (2), DVT (2)</td>
</tr>
<tr>
<td>Italian ward (327)⁷</td>
<td>LMWH (in 75%)</td>
<td>20 (6.1)</td>
<td>PE (7), DVT (2), SVT (2), MI (3), stroke (6)</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus disease of 2019; CRRT, continuous renal replacement therapy; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LMWH, low molecular-weight heparin; MI, myocardial infarction; PE, pulmonary embolism; SVT, superficial vein thrombosis; UFH, unfractionated heparin.

¹ Patients were screened for DVT. ¹ Only reported PE.

COVID-19: Real-World Experience

COVID-Associated Coagulopathy1-6

- ↑ D-Dimer
- ↑ Fibrinogen
- ↑ C reactive protein
- ↑ Factor VIII
- ↑ Von Willebrand factor
- Lupus anticoagulant
- TEG changes (↑ R-time, ↓ K-time, ↑ MA, ↓ LY30)

Minor or no effect on:
- Platelet count
- Prothrombin time
- Antithrombin/Protein C/Protein S levels

Pathophysiology: Virchow’s Triad

- Circulatory stasis
  - Intravascular access devices
  - Invasion of endothelial cells?
  - Complement?
- Immobilization
  - ↑ FVIII
  - ↑ Fibrinogen
  - ↑ NETs
  - Relevance of LA?

Thrombosis

Endothelial injury

Hypercoagulable state

Treatment Intensity Recommendations7-9

<table>
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<th></th>
<th>Non critically ill</th>
<th>Critically ill</th>
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<tr>
<td>ISTH</td>
<td>Prophylactic</td>
<td>Prophylactic</td>
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<tr>
<td>AC forum</td>
<td>Prophylactic</td>
<td>Intermediate</td>
</tr>
<tr>
<td>NIH</td>
<td>Prophylactic</td>
<td>Prophylactic</td>
</tr>
</tbody>
</table>

Prophylactic-intensity regimens: enoxaparin 40 mg daily, UFH 5000 U SC BID or TID.
Intermediate-intensity regimens: enoxaparin 40 mg BID, enoxaparin 0.5 mg/kg BID, UFH 7500 U SC TID

BID, twice daily; COVID-19, coronavirus disease of 2019; CRP, C-reactive protein; K-time, amplification time; LA, lupus anticoagulant; LY30, measure of clot stability; MA, maximum amplitude; NET, neutrophil extracellular traps; R-time, initiation time; SC, subcutaneously; TEG, thromboelastography; TID, 3 times daily.

Take-home Points

- Thrombotic manifestations of COVID-19 include VTE, pulmonary microvascular thrombosis, and, less commonly, arterial thrombosis.

- VTE is common in ICU patients (≈20%-40%) despite prophylactic-intensity anticoagulation.

- Potential mechanisms include immobilization, hypercoagulability, and endothelial injury.

- Clinical trials are needed to determine whether increasing the intensity of anticoagulation is effective and safe.

- Current clinical guidance is mixed on whether patients in the ICU should receive increased-intensity anticoagulation.