**DISCLOSURES FOR:**
**MARILYN J. MANCO-JOHNSON**

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tbody>
<tr>
<td>Research Support</td>
<td>Bayer, CSL Behring</td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td></td>
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<tr>
<td>Shareholder</td>
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<td>Honoraria</td>
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<td>Advisory Committee</td>
<td>Baxter, Bayer, BiogenIdec, CSL Behring, NovoNordisk</td>
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<td>Consultant</td>
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IS THE ANNUAL BLEEDING RATE ENOUGH?

THE MICROPATHOLOGY OF JOINTS

Montreal

September 26, 2013
Is the annual bleeding rate enough in the age of prophylaxis?
WHAT ARE THE IMPORTANT ADVERSE OUTCOMES IN HEMOPHILIA?

Outcomes related to Hemophilia
1. Fatal hemorrhage
2. Intracranial or retroperitoneal hemorrhage
3. Crippling arthropathy

Outcomes related to therapy
1. Inhibitor formation
2. Pathogen transmission
What defines joint bleeding?

**CLINICAL (CLASSIC)**

**PATIENT REPORT:**
- SENSATION: TINGLING, WARMTH, PAIN

**PHYSICAL EXAMINATION**
- DECREASED RANGE OF MOTION
- SWELLING
- EXTERNAL WARMTH

**PATHOPHYSIOLOGICAL (RECENT)**

**IMAGING:**
- FLUID COLLECTION
- HEMOSIDERIN DEPOSITION
- SYNOVIAL THICKENING

**MOLECULAR/HISTOLOGIC:**
- EXPRESSION OF PROLIFERATIVE AND INFLAMMATORY CELLULAR MARKERS AND LIGANDS
- ALTERATION OF BONE AND CARTILAGE BLASTIC/CLASTIC ACTIVITY
What defines hemophiliic arthropathy?

CLINICAL (CLASSIC)

PHYSICAL EXAMINATION:
- FIXED FLEXION AND EXTENSION CONTRACTURES
- MUSCLE ATROPHY AND WEAKNESS
- BONY OVERGROWTH
- JOINT INSTABILITY

IMAGING (RECENT)

MRI:
- SUBCHONDRAL EROSIONS
- BONE CYSTS
- CARTILAGE NARROWING AND LOSS
- OSTEOPOROSIS
WHAT EVIDENCE RELATES THE ANNUALIZED BLEEDING RATE TO ARTHROPATHY?
The Orthopedic Outcome Study: Joint deterioration is less when clinical bleeding rate is decreased

<table>
<thead>
<tr>
<th>Infusion Schedule</th>
<th>Prophylaxis N = 66</th>
<th>On-Demand N = 411</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Bleeds/year</td>
<td>9.49</td>
<td>25.5</td>
</tr>
<tr>
<td>Change in WFH Score/year</td>
<td>1.00</td>
<td>3.05</td>
</tr>
</tbody>
</table>

Secondary Prophylaxis to Prevent Joint Deterioration: WFH PE scores can improve & XR scores may stabilize when clinical bleeding rate is decreased.

<table>
<thead>
<tr>
<th></th>
<th>WFH Physical Joint PE core</th>
<th>Pettersson X-Ray Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Stabilized</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Progressed</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

16 affected joints in 13 boys, mean age 6.9 (range 2-12 years); 12 severe FVIII; 2 Maintenance phase IT

WHAT EVIDENCE SUGGESTS THAT NUMBER OF CLINICALLY DETERMINED JOINT HEMORRHAGES MAY NOT ACCOUNT COMPLETELY FOR ARTHROPATHY?

I. Joint Outcome Study (JOS)
II. Universal Data Collection Project (UDC)
III. Meta-analysis of MRI studies in hemophilia
IV. Joint Outcome Continuation Study (JOS C)
I. THE JOINT OUTCOME STUDY 1995-2005

- RCT of prophylaxis (routine infusions of FVIII 25 U/kg qod) vs enhanced episodic therapy (an augmentation of standard on demand with $\geq 3$ infusions/joint bleed) in 65 boys with severe Hem A
- Enrollment & treatment arm initiated prior to 30 months of age
- Outcome determined at age 6 years
- Primary outcome: joint structure by MRI of both elbows, knees and ankles
- Secondary outcomes: joint function by physical exam, number of joint and total bleeding events, factor utilization
- Joint bleeding events were clinically determined
- JOS funding CDC; rFVIII given Bayer HealthCare
Compared with Prophylaxis, RR for Joint Damage on Enhanced Episodic = 6.29 (CI 1.6-26.6) using MRI outcome
Prophylaxis → 84% relative risk reduction
MRI and XR: 86% agreement
JOS: CORRELATION OF MRI OUTCOME WITH CUMULATIVE # OF HEMARTHROSES

N = 346 Joints
r = .36
R² = 0.13

MRI Showed Modest Correlation with # of Hemarthroses

JOINT FAILURE INDICATED BY MRI SCORE 7-10 (OSTEOCHONDRAL DEFECTS)
a) MRI evidence of osteochondral defects are only partially explained by clinically evident hemarthroses.

b) Osteochondral defects in the absence of overt bleeding history primarily seen in the episodic arm.

c) Microbleeding or oozing into joints of children not on prophylaxis could explain abnormal MRI findings; routine replacement of FVIII interrupts microbleeding.

d) Other effects of FVIII deficiency on cartilage and bone matrix, osteoclastic activity or inflammation are possible.
II. UNIVERSAL DATA COLLECTION PROJECT (UDC) 1998-2010

A US Public Health Service initiative directed by the US Congress; funded and implemented through the CDC with the USHTCN

Collected serial data on 26,614 visits for 6,194 males with severe hemophilia A

12 years of data collection, 1999-2010

Data collected on bleeding rates, indicators of arthropathy and other outcomes

Analyses were made of arthropathy, as indicated by percentage loss of joint range of motion, in comparison to various clinical factors
Correlates of arthropathy in 3368 boys with hemophilia ages 2-19 yrs.

Repeated measures of overall joint range of motion in 3,368 U.S. hemophilia participants aged 2-19 years.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Initial ROM status</th>
<th>Rate of ROM change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Parameter estimate</td>
<td>p value</td>
</tr>
<tr>
<td>Age</td>
<td>-0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race: White vs. others</td>
<td>1.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inhibitor: yes vs. no</td>
<td>-0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI: ≥85th vs. &lt;85th percentile</td>
<td>-1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary prophy: yes vs. no</td>
<td>0.71</td>
<td>0.30</td>
</tr>
<tr>
<td>Secondary prophy: yes vs. no</td>
<td>0.55</td>
<td>0.36</td>
</tr>
</tbody>
</table>
INTERPRETATION OF THE UDC DATA IS COMPLEX:

Joint ROM on initial evaluation:

1. In this registry, most participants on primary prophylaxis were in the first decade of life. Therefore, joint range of motion was preserved both in young participants using or not using primary prophylaxis, and no statistical difference was seen between groups.

2. Factors significant in predicting decreased range of motion including increasing age and positive inhibitor status, were likely mediated through bleeding.

3. Non-white race may convey an increased risk for disparate access to health care with increased bleeding.
INTERPRETATION OF THE UDC DATA IS COMPLEX:

Joint ROM on serial evaluations:
1. ROM preservation was highly associated with primary prophylaxis
2. ROM preservation showed a trend toward significance with secondary prophylaxis
3. The effect of obesity is seen on the initial and serial evaluations
Data are suggestive that preservation of joint function in severe hemophilia A as measured by joint range of motion is most highly correlated with primary prophylaxis which is a surrogate for:

a) Prevention of joint bleeding from an early age

b) Routine replacement of factor VIII from an early age
III. META-ANALYSIS OF JOINT MRI IN HEMOPHILIA 2011-2014

Inclusion of data from 3 separate studies

Individual participants aggregated into a single data base

Only data elements common to all 3 studies used

MRI and PE data converted to a single scale across studies: MRI 45 point scale; PE WFH scale

Data analyzed by total subject score, and also per individual joint score

Analyses segregated participants treated only with on-demand from participants who had received prophylactic therapy

Meta-analysis studies funded by CDC; data from Spinart and the European Study provided by Bayer
ANNUALIZED BLEEDING RATE DOES NOT PREDICT JOINT OUTCOME IN HEM A TREATED USING ON-DEMAND DEMAND

CORRELATION OF TOTAL SUBJECT MRI SCORE WITH ANNUALIZED BLEEDING RATE WAS NOT SIGNIFICANT

3 STUDIES OF INDIVIDUALS WITH NO HISTORY OF PROPHYLAXIS
IV. THE JOS CONTINUATION 2009-2017

Original participants of JOS are recruited to a follow-up study

Treatment beyond age 6 years clinically prescribed

Most children on the early prophylaxis arm remained on prophylaxis

Most children on the enhanced episodic arm adopted prophylaxis at the time that study results were disclosed

Data includes infusion logs from birth, joint PE, activities, QoL and MRI/XR every 4 years until age 18.

Mean age at first follow-up 13 years

JOS C is funded by Bayer HealthCare
<table>
<thead>
<tr>
<th>Regression Model</th>
<th>MRI score</th>
<th>bleeds</th>
<th>Early prophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) MRI = Tx</td>
<td>Outcome</td>
<td>-9.43 ( -17.85, -1.01)</td>
<td>0.0409</td>
</tr>
<tr>
<td>(b) Bleeds = Tx</td>
<td></td>
<td>-15.50 ( -32.98, 1.98)</td>
<td>0.0984</td>
</tr>
<tr>
<td>(c) MRI = bleeds</td>
<td>Outcome</td>
<td>0.21 ( 0.01, 0.42)</td>
<td>0.0560</td>
</tr>
<tr>
<td>(d) MRI = bleeds + Tx</td>
<td>Outcome</td>
<td>0.15 ( -0.06, 0.36)</td>
<td>0.1845</td>
</tr>
</tbody>
</table>

Note: MRI = Magnetic Resonance Imaging, bleeds = Bleeding events, TX = Treatment
JOS C PER-JOINT ANALYSIS: ANNUALIZED BLEEDING RATE IS LESS SIGNIFICANT WHEN TREATMENT IS INCLUDED IN ANALYSIS MODEL

<table>
<thead>
<tr>
<th>Regression</th>
<th>MRI score</th>
<th>bleeds</th>
<th>Early prophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) MRI = Tx</td>
<td>Outcome</td>
<td></td>
<td>-1.56 (-2.56, -0.56) 0.0027</td>
</tr>
<tr>
<td>(b) Bleeds = Tx</td>
<td>Outcome</td>
<td></td>
<td>-2.55 (-4.83, -0.26) 0.0306</td>
</tr>
<tr>
<td>(c) MRI = bleeds</td>
<td>Outcome</td>
<td>0.20 ( 0.13, 0.27) 0.0000</td>
<td></td>
</tr>
<tr>
<td>(d) MRI = bleeds + Tx</td>
<td>Outcome</td>
<td>0.19 ( 0.11, 0.26) 0.0000</td>
<td>-1.09 (-2.02, -0.16) 0.0227</td>
</tr>
<tr>
<td>By Participant</td>
<td>By Joint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>All participants: 0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early prophy</td>
<td>Early prophy: 0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed prophy</td>
<td>Delayed proph: 0.32</td>
<td></td>
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</table>
DOES THE ANNUALIZED BLEEDING RATE COUNT?

Of course, it does. Bleeding does not portend a good outcome in severe hemophilia.

However, clinical joint hemorrhage in the annualized bleeding rate accounts for some, but not all, of the structural damage imaged by MRI in persons with severe hemophilia.
DOES THE ANNUALIZED BLEEDING RATE COUNT?

Prophylaxis mitigates some of the MRI damage demonstrated in persons using on-demand therapy, and the mitigation seems to be primarily that of the non-clinical or “micro” bleeding, or “oozing”.

These data alter the conversation around individually tailored prophylaxis insofar as they suggest that not all important bleeding events can be clinically appreciated.
ACKNOWLEDGEMENTS

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Associate Director for Science, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

Bayer HealthCare, esp Walter Hong, MD and Tom Humphries, MD