2012 CME/CE NetWorkShops™
Clinical Challenges in Your Hemophilia Treatment Center
Faculty Presenters

Miguel A. Escobar, MD
Associate Professor
Department of Pediatrics and Internal Medicine
Division of Hematology
The University of Texas Health Science Center at Houston
MD Anderson Cancer Center
Medical Director, Gulf States Hemophilia and Thrombophilia Center
The University of Texas-Houston Medical School
Houston, Texas

Patrick F. Fogarty, MD
Director, Penn Comprehensive Hemophilia and Thrombosis Program
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
Faculty Presenters

Mark T. Reding, MD
Associate Professor of Medicine
Division of Hematology, Oncology, and Transplantation
Director, Center for Bleeding and Clotting Disorders
University of Minnesota Medical Center
Minneapolis, Minnesota

Leonard A. Valentino, MD
Professor
Rush University Medical Center
Chicago, Illinois

Tammuella Chrisentery Singleton, MD
Marcelle Schaefer Vergara Chair in Pediatric Hematology/Oncology
Assistant Professor of Pediatrics
Tulane University School of Medicine
Louisiana Center for Bleeding and Clotting Disorders
Tulane Hospital for Children
New Orleans, Louisiana
Program Outline

• Bypassing Therapy and Inhibitors
• Immune Tolerance Induction
• Prophylaxis and Reduction of Hemophilic Arthropathy
  ▪ Case discussion
• Outcomes and Health-Related Quality of Life
• Acquired Hemophilia
Learning Objectives

• Discuss new clinical data from scientific posters, abstracts, and published articles about hemophilia and their bearing on clinical practice

• Assess evidence and expert commentary regarding diagnosis, treatment, and management of hemophilia with inhibitors

• Differentiate between therapeutic options for patients with severe hemophilia who have or are at risk for developing inhibitors

• Integrate expert recommendations concerning a case study into patient management strategies

• Provide appropriate care and counsel for patients and their families
Bypassing Therapy and Inhibitors
Study Rationale and Objectives

• Secondary prophylaxis shown to decrease frequency of acute bleeding episodes
  ▪ May potentially delay progression of hemophilic arthropathy in inhibitor patients

• Objective: To evaluate the effectiveness and safety of rFVIIa prophylaxis in hemophilia patients with inhibitors
• International, retrospective, observational study

• 86 patients with hemophilia and inhibitors treated with rFVIIa prophylaxis for ≥30 d
  ▪ Median age 6 y
    • Range 0.1-52 y; 71% pediatric (<12 y)
  ▪ Dosing schedules
    • 3x/wk, median dose 197 µg/kg
    • OD, median dose 136 µg/kg
Study Results

- Median prophylaxis duration 288 d (range 22-3651 d)
  - Most patients (n=79, 92%) received prophylaxis for prevention of recurrent bleeding
  - Overall bleeding reduction 46% vs pre-prophylaxis period
  - 52% reduction in bleed frequency
  - 57% reduction in target joint bleeds among patients who experienced ≥1 bleed/month pre-prophylaxis
  - 57% reduction in bleeds/month in pediatric patients with frequent bleeds
- No thromboembolic events (TEs) or deaths reported
- Burden of disease (hospital admissions, length of stay) observed to be reduced during prophylaxis
Study Conclusions

• Pediatric patients on 3x/wk dosing showed similar bleed reduction as those on daily dosing

• Clinically relevant reductions in bleed frequency and favorable safety profile suggest the benefits of prophylaxis rFVIIa in a selected population of hemophilia patients with inhibitors
Patients with hemophilia A and inhibitors are at risk for serious bleeding and joint complications that ultimately may impact health-related quality of life (HRQoL).

Study purpose: To evaluate safety and efficacy of an anti-inhibitor coagulant complex (FEIBA) for bleeding prophylaxis in hemophilia A patients >2 y with high-responding inhibitors.
Study Design and Methods

- Prospective, randomized, crossover study compared 6 months of prophylaxis with 6 months of on-demand treatment with FEIBA, separated by 3-month washout.

- Dose: 85 U/kg both study arms
- Prophylaxis administered on 3 non-consecutive days per week
Study Results

- 34 patients underwent randomization
- 26 patients completed both treatment periods
- Prophylaxis associated with a 62% reduction in all bleeding episodes, a 61% reduction in hemarthroses, and a 72% reduction in target joint bleeding
Safety Data and Conclusion

- 34 AEs reported
  - No TEs
  - One allergic reaction deemed related to study drug
- 1 patient in washout period and 1 patient in prophylaxis treatment arm died of complications associated with underlying illness and bleeding
- Conclusion: FEIBA, dosed at 85 U/kg (±15%), significantly and safely decreased the frequency of joint and other bleeding events in patients with severe hemophilia A and inhibitors
Clinical Application: Polling Question 1

How many patients at your HTC receive prophylaxis with bypassing agents?

a) 0
b) 1
c) 1-3
d) 3-5
e) >6
Immune Tolerance Induction
Study Background and Rationale

- Immune tolerance induction (ITI) proven successful in eradicating inhibitors in majority of patients with severe hemophilia A
- For minority of patients, ITI ineffective
- Higher incidence of inhibitors in African American patients with hemophilia compared with other hemophilia patient groups
- Identification of factors that identify patients less likely to be tolerized may be helpful in identifying patients who may benefit from new ITI approaches
- Study design and purpose: Single-center chart review conducted over 17-year period to identify factors potentially associated with poorer chance of success with ITI
Patients and Methods

• Study population: 31 boys with severe hemophilia A and inhibitors who underwent 35 courses of ITI
  ▪ 8 courses of ITI in Caucasians (22.9%)
  ▪ 23 courses in African Americans (65.7%)
  ▪ 4 courses in Middle Easterners (11.4%)
• Dosing
  ▪ For low-responding inhibitors FVIII 50 U kg/day 3-4x/wk
  ▪ For high-responding inhibitors FVIII 50-250 U kg/day
Study Results

• 31 completed courses of ITI
  ▪ 22 patients (71%) achieved complete tolerance
  ▪ 9 courses of ITI failed
  ▪ 4 patients continue on therapy

• Length of successful course no different between African American and non–African American patients (229.8 vs 152.4 days, \( P=0.49 \))
  ▪ However, ITI courses less likely to be successful in African Americans versus non–African Americans (57.9% vs 92%, respectively; \( P=0.04 \))
    ▪ Difference largely due to higher inhibitor titers at start of ITI in African Americans
### Differences in Predictive Variables for Immune Tolerance Induction Among African American and Non–African American Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>African American</th>
<th>Non–African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical peak (BU mL(^{-1}))</td>
<td>175.7</td>
<td>37.3</td>
</tr>
<tr>
<td>Start ITI (BU mL(^{-1}))</td>
<td>35.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Peak on ITI (BU mL(^{-1}))</td>
<td>196.5</td>
<td>80.3</td>
</tr>
<tr>
<td>Time to tolerance (days)</td>
<td>229.8</td>
<td>152.4</td>
</tr>
<tr>
<td>Age at start of ITI (months)</td>
<td>65.2</td>
<td>95.9</td>
</tr>
<tr>
<td>Age at inhibitor development (months)</td>
<td>15.6</td>
<td>37.1</td>
</tr>
<tr>
<td>Exposure days prior to inhibitor</td>
<td>7.8</td>
<td>18.7</td>
</tr>
</tbody>
</table>

Study Results (cont)

- Trend toward earlier development of inhibitors in ITI failures
  - Mean age at inhibitor development 1 y 3 mo in failures versus 2 y 4 mo in successfully tolerized patients
- High inhibitor titer at start of ITI associated with failure
  - 7/11 ITI trials with titers >10 BU resulted in failure
  - 15/17 ITI trials with titers <10 BU were successful
Conclusions: Risk Factors for Unsuccessful ITI

- African American race
  - Genetic variables such as cytokine polymorphisms or FVIII haplotype potentially play a role
- High historical peak inhibitor titers
- Higher inhibitor titer at initiation of ITI
- Early age at diagnosis of inhibitor
Prophylaxis and Reduction of Hemophilic Arthropathy
Clinical Application: Polling Question 2

Among your patients with severe hemophilia A and no inhibitors, how many bleeding episodes within a 6-month period generally have precipitated a change in treatment from on-demand to prophylaxis?

a) 1-3
b) 4-6
c) 7-12
d) Number of bleeds has no impact on whether a switch is made
Background and Objective

- Hemophilic arthropathy debilitating result of recurrent hemarthrosis
- Prophylaxis provides immediate benefit and improves long-term disease prognosis in severe hemophilia
- Published evidence suggests that prophylaxis prevents joint damage and reduces frequency of joint hemorrhage in severe hemophilia and is associated with markedly better QoL compared with on-demand treatment (Manco-Johnson et al, 2007; Aledort et al, 1994; Berntorp, 2009; Gouw et al, 2007)
- Study objective: Note discrepancies between published clinical evidence and current treatment practices for patients with hemophilia A using findings from practice patterns documented in 2010 Practice Patterns Survey (PPS) of hemophilia treatment in the United States
  - Nurses’ estimates used to determine incidence of bleeding episodes
Study Results

• PPS documented 7683 patients at 71 HTCs in United States
  - 3881 patients had severe disease
  - 1649 pediatric patients
  - 2232 adult patients
  - 2600 patients received primary or secondary prophylaxis
Use of prophylaxis continues to increase among patient population

- Since 2003, use of primary prophylaxis increased most among patients $\geq$ 13 y
- Since 2003, the use of on-demand treatment has declined the most among patients $\geq$ 18 y, compared with other age-groups
Switch in Treatment Type

- Most patients who switched from on-demand to prophylaxis were infants $\leq 2$ y
- Most patients who switched from prophylaxis to on-demand were aged 13-24 y
  - High proportion of patients experienced $\geq 7$ bleeding episodes during 6-month period while receiving on-demand treatment
- 48% of patients aged 13-24 y switched to prophylaxis after experiencing 4-6 bleeds in a 6-month period
Patients With Severe Hemophilia A Without Inhibitors Who Switched Treatment Type in 2009

Patients Who Switched From On-Demand Treatment to Prophylactic Therapy

<table>
<thead>
<tr>
<th>Patient Age (y)</th>
<th>Patients (%)</th>
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</thead>
<tbody>
<tr>
<td>0-2</td>
<td>21</td>
</tr>
<tr>
<td>3-12</td>
<td>4</td>
</tr>
<tr>
<td>13-17</td>
<td>3</td>
</tr>
<tr>
<td>18-24</td>
<td>3</td>
</tr>
<tr>
<td>25-44</td>
<td>3</td>
</tr>
<tr>
<td>45-64</td>
<td>3</td>
</tr>
<tr>
<td>≥65</td>
<td>1</td>
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Patients Who Switched From Prophylactic Therapy to On-Demand Treatment

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<th>Patient Age (y)</th>
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<tr>
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</tr>
<tr>
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<tr>
<td>18-24</td>
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<tr>
<td>45-64</td>
<td>1</td>
</tr>
<tr>
<td>≥65</td>
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</table>
Study Conclusions

• Published findings reveal benefits of prophylaxis for preventing hemorrhage and subsequent development of arthropathy

• Data from PPS show that despite increased use of prophylaxis, patients do not switch from on-demand until they have experienced a minimum of 4-5 bleeds in a 6-month period

• Patients aged 13-24 y most likely to switch from prophylaxis to on-demand

• Data suggest that despite clinicians’ recommendations, patients do not understand importance of continuing with and adhering to prophylaxis

For more information on this subject, please visit the Blood CME Center to view a relevant activity, “Transitioning From Pediatric to Adult Hemophilia Care: Managing Lifestyle and QoL Challenges”
Study Design and Methods

- Observational, prospective, case-controlled, multicenter study
- Objective: To evaluate bleeding and QoL in patients with severe hemophilia A relative to discontinuation of long-term prophylaxis
  - 38 adolescent/young adult patients (14-29 y) enrolled into either 2 prospective or 1 retrospective group
    - Continuous prophylaxis (n=22)
    - Discontinued prophylaxis for \( \leq 12 \) mo (n=5)
    - Discontinued prophylaxis for \( > 12 \) mo (n=11)
    - rFVIII prophylaxis 20-50 IU/kg \( \geq 2x/wk \), minimum of 5 y
• Primary outcomes: Bleeding rate documented by electronic logs, QoL, and number of patients returning to prophylaxis

• Secondary and exploratory variables
  - Gilbert score
  - Target joints
  - Hemophilia Activities List (HAL)
  - Godin Leisure Time
  - State Trait Anxiety Inventory (STAI)
Results and Conclusions

- Significant increase in bleeding rates and decrease in QoL after discontinuing prophylaxis
- With increased time off prophylaxis, scores for both bleeding rates and QoL worsened
- Data suggest benefits of regular prophylaxis in reducing number of bleeding events
Clinical Application: Polling Question 3

How do you increase awareness among your adolescent patients about the importance of adhering to prophylactic treatment regimens?

a) I rely on members of the hemophilia care team, including social workers and physical therapists, to help reinforce the benefits of prophylaxis

b) I ensure that my patients have access to transitional care services

c) I use social media portals such as Facebook, YouTube, and CaringBridge to stay better connected with my patients

d) All of the above

e) None of the above
Are there protocols in place at your HTC to help prepare your pediatric/adolescent patients for the transition to adult care?

a) Yes
b) No
c) Not yet, but they are in development
• DQ is a 17-year-old with severe hemophilia A who is preparing for his first year of college
• History of right knee bleeding as a toddler, which abated after starting prophylaxis with rFVIII
• In the last year, annual bleeding rate was 4, with only 1 right knee bleed
• During the visit, discussion regarding the importance of continuing prophylaxis and adherence to the treatment regimen emphasized
• Recommendation to continue every-other-day prophylaxis and regular exercise
Faculty Case (cont)

- After 3 months, patient returns for fall break; parents are concerned because of limping and right knee swelling
- DQ admits to missing many prophylaxis doses and playing tackle football with roommates. After joint bleeding, did not promptly infuse factor
- Right knee warm to touch, with boggy swelling and reduced ROM
- Recommendation is to resume prophylaxis and reinforce the need for prompt treatment of acute bleeding
Outcomes and Health-Related Quality of Life
Study Aims and Methods

- To assess levels of HRQoL in patients with severe hemophilia and compare HRQoL to that of general population
- To determine whether reduced bone density correlates with perceived HRQoL
- Study population: 39 adult patients with severe hemophilia A or B and no history of inhibitors
- Patients divided into 2 groups based on timing of prophylaxis
  - Group A: prophylaxis initiated at age \( \leq 3 \) years
  - Group B: prophylaxis initiated at age \( >3 \) years
- Bone density assessment: DXA scan
- HRQoL: SF-36
Results

• Mean BMD T-score normal (> -1.0) at all measured sites for group A and almost similar scores in SF-36 domains compared with general population

• Mean BMD T-score <-1.0 at hip region and > -1.0 at lumbar spine and total body for group B and lower SF-36 scores compared with general population
Study Conclusions

- Hemophilia patients who initiated prophylaxis in early childhood reported comparable BMD and HRQoL with general population.
- Hemophilia patients who did not start prophylaxis by age 3 years perceived poorer physical health than general population.
Acquired Hemophilia
Ma AD, Kessler CM, Gut RZ, Cooper DL. Recombinant factor VIIa (rFVIIa) is safe and effective when used to treat acute bleeding episodes and to prevent bleeding during surgery in patients with acquired hemophilia: updated assessment from the Hemostasis and Thrombosis Research Society (HTRS) registry AH database. Presented at: 53rd Annual Meeting and Exposition of the American Society of Hematology (ASH); December 10-13, 2011; San Diego, CA. Abstract 3374.
Background and Methods

- Acquired hemophilia is a rare disorder but has associated mortality of 8%-22%
- Characterized by development of autoantibodies to FVIII
- Clinical presentation includes bleeding episodes or unexpected bleeding during surgery
- Prolonged aPTT does not correct with 1:1 mixing
- Treatment includes inhibitor eradication with immunosuppression or hemostatic therapy with bypassing agents to resolve bleeding or prevent bleeding during surgery
- Study Methods: Analysis of Hemostasis and Thrombosis Research Society (HTRS) registry surveillance data for rFVIIa (January 2004-July 2011)
Results

- 154 patients
  - 99 had 217 bleeds
  - 35 underwent 56 surgical procedures
- Use of rFVIIa
  - 125 rFVIIa-treated bleeds
- Mean age at bleeding, 66 y

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose (mcg/kg)</th>
<th>Average Dose Per Injection (mcg/kg)</th>
<th>Total Dose Per Episode (mcg/kg)</th>
<th>Number of Injections</th>
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</thead>
<tbody>
<tr>
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<td>90</td>
<td>360</td>
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</tr>
<tr>
<td>Range</td>
<td>13-270</td>
<td>16-270</td>
<td>30-18,000</td>
<td>1-240</td>
</tr>
</tbody>
</table>
Results (cont)

- 56 surgical procedures
  - 24 rFVIIa-treated
  - 17 rFVIIa only
    - Mean age, 72.4 y
    - Mostly female, white, non-Hispanic

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose (mcg/kg)</th>
<th>Average Dose Per Injection (mcg/kg)</th>
<th>Total Dose Per Episode (mcg/kg)</th>
<th>Number of Injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
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<td>96</td>
<td>399</td>
<td>4</td>
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<tr>
<td>Range</td>
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<td>53-200</td>
<td>75-6229</td>
<td>1-77</td>
</tr>
</tbody>
</table>
Efficacy and Safety

- Overall physician-reported efficacy, 97%
- 1 TE reported in postpartum patient with transient neurologic symptoms
Conclusions

- HTRS registry second largest data set reporting rFVIIa use in acquired hemophilia
  - 75% increase in rFVIIa-treated bleeds in past 2 years
- No safety concerns reported
- Data indicate that rapid and safe hemostasis can be obtained with rFVIIa for acute bleeding episodes and prevention of excessive perioperative bleeding in aging population
For additional programs on hemophilia and blood-related disorders, please visit:

www.bloodcmecenter.org