Issues and Challenges in Your Hemophilia Treatment Center
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CME Information

Target Audience
This activity has been designed to meet the educational needs of hematologists, physicians, physician assistants, nurse practitioners, registered nurses, physical therapists, social workers, and other specialists of the hemophilia treatment center (HTC) team, as well as clinicians interested in the treatment and management of patients with hemophilia.

Statement of Need
Hemophilia is the most common and severe inherited bleeding disorder recognized in humans and comprises the largest proportion of patients managed in most bleeding disorder clinics and HTCs. For many practicing clinicians, there is neither time nor opportunity to attend the major national and international society meetings to gain insights into a range of clinical challenges and patient management issues frequently encountered in the HTC setting.

With the CME/CE NetWorkShops™ series, however, these meetings can be brought to busy clinicians in the form of webcasts and organized group workshops at or near HTCs. Healthcare professionals are now able to view, analyze, and discuss key meeting findings with recognized hemophilia experts while gaining ideas on how to apply new learning to their own clinical practice.
Learning Objectives

• Discuss selected scientific posters, abstracts, and published articles on topical issues in hemophilia, including burden of illness, morbidity, and dosing strategies
• Compare treatment strategies, including immune tolerance induction, for patients with hemophilia A and inhibitors
• Describe bleeding phenotype and characteristics of anti-factor VIII autoantibodies in acquired hemophilia
• Develop management strategies to minimize joint damage in patients with severe hemophilia A
• Provide appropriate care and counsel for hemophilia patients and their families
HTC CME/CE NetWorkShops™: Program Outline

- Hemophilia Morbidity
  - Case discussion
- Acquired Hemophilia A
- Hemophilia B
- Treatment Strategies
- Interactive Q & A
Hemophilia Morbidity
Valentino LA, Forsyth A, Guelcher C, Witkop M, Lambing A, Cooper DL.

Is bleeding in hemophilia really spontaneous or activity related: analysis of US patient/caregiver data from the Hemophilia Experiences, Results and Opportunities (HERO) study.

Poster presented at: 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA.
Study Background

• Bleeding in hemophilia is thought to transition from traumatic cases in early childhood to more spontaneous bleeding in adolescents and adults, with development of target joints and progression of arthropathy.

• In this overall analysis of psychosocial issues affecting children and adults with hemophilia, HERO investigators also examined:
  – Reported bleed frequency/location
  – Most affected joint
  – Bleeding causes
  – Current employment and activities
Methods

• 10-country survey
• People with hemophilia (PWH) ≥18y
• Parents of children with hemophilia <18y
• Characteristics of US participants
  – 189 PWH (age range 18-74y)
  – 190 parents of children with hemophilia

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
</tr>
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<tbody>
<tr>
<td>Hemophilia A</td>
<td>59%</td>
<td>66%</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>Hemophilia w/ Inhibitors</td>
<td>24%</td>
<td>9%</td>
</tr>
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</table>
Results

- Over the previous 12 months, PWH on secondary prophylaxis reported roughly the same number of bleeds requiring treatment compared to those receiving on-demand therapy.
- More unemployed PWH reported a specific joint affected by hemorrhages
  - Ankle most frequently cited
- Repetitive activity reported as most common cause of most recent hemorrhage in patients on prophylaxis
  - More common in those working (40%) than unemployed (22%)
  - Spontaneous bleeding most common in unemployed (46%) and those aged ≥41y (41%)
Results (cont)

Figure 1. Cause of last hemorrhage in adult PWH

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Employed</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-demand</td>
<td>Trauma</td>
<td>≤30</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Repetitive activity</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Results (cont)

- Parents most often reported their child’s last hemorrhage caused by trauma (49%) vs spontaneous hemorrhage (27%) or repetitive activity (18%)
- Trauma and repetitive activities combined were the most common causes of last hemorrhage in children
Conclusion

• HERO provides unique insights into the causes of bleeding in adults and children with hemophilia
• Addition of the “repetitive activity” category in HERO study as reflection of non-traumatic work/school/sports activity suggests the possibility of triggers for bleeding previously described as “spontaneous”
  – Further attention warranted by HTC team, including the PT
  – Further investigation required
Clinical Application

• Not all patients are the same!
  – Causes of and patterns of bleeding vary, depending on age, activity level and type, and treatment regimen
  – With aging, joint status and other co-morbidities may also influence bleeding patterns
  – Need to individualize treatment plans
Patient Profile

- 18-month-old male
- Diagnosed with severe hemophilia at 3 days of age
  - FVIII level <1%
  - No inhibitors
- Uncomplicated neonatal period

Medical History

- No comorbidities
- Receives on-demand treatment with factor replacement

Treatment and Bleeding History

- Episodic treatment with rFVIII concentrate
  - First treatment at 8 months of age for minor wrist bleed; good response to therapy
  - Since the patient started walking, at 12 months, he has experienced extensive bruising and hematomas, primarily involving both knees, and 1 traumatic oral bleed
  - His venous access is poor, so most of his bleeding manifestations have been managed conservatively
- Presents to clinic with first bleed involving his right knee. No identifiable trauma, according to parent
Questions to Consider

• Should prophylaxis be initiated now for this patient?
• What aspect of this case offers the most compelling reason for prophylaxis? For continued on-demand treatment?
• To what degree should venous access issues play a role in the determination of a treatment strategy?

Long-term orthopedic effects of delaying prophylaxis in severe hemophilia A until age 6 years: results of the Joint Outcome Study continuation (JOSc).

Abstract presented at: 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA.
• Randomized controlled clinical trial in boys with severe FVIII deficiency
  – Compared every-other-day prophylaxis (25 IU/kg FVIII) begun prior to age 30 months with enhanced episodic therapy given only in response to bleeding
  – 6 index joints (ankles, knees, elbows) assessed by physical exam and MRI at study exit (age 6)
  – JOS demonstrated superiority of prophylaxis over episodic treatment
  – At JOS end, parents informed of results and boys in episodic arm counseled to start prophylaxis
Purpose of JOS Continuation

• Determine effect of early prophylaxis on joint development until age 18y
• Determine impact of delaying prophylaxis initiation until age 6y
  – All but 1 subject in the episodic arm started prophylaxis at JOS end
Methods

- Study data collection
  - Cumulative number of index joint and total hemorrhages
  - Joint physical examination (PE) score of 6 index joints
  - MRI soft tissue, osteochondral, and total scores of 6 index joints
  - Prophylaxis adherence, activities, surgeries, QoL, and factor utilization
Subjects

- 26/65 (40%) boys from original study analyzed
  - 16 on early prophylaxis
  - 10 on delayed prophylaxis
- 156 index joints available for analysis
Results / Conclusion

• Although still enrolling, the JOS continuation study is documenting an ongoing disparity in joint outcome in children who delayed initiation of prophylaxis until age 6 years compared with those who started prophylaxis before age 30 months.

• Following delayed initiation of prophylaxis, adolescents demonstrate increased numbers of hemarthroses and increased joint, bone, and soft tissue damage on MRI.
Clinical Application

- This study builds on the findings of JOS
- Benefits of early prophylaxis continue long beyond initial treatment period
- Supports the notion that early prophylaxis is the best way we currently have to minimize joint damage over the long term in those with severe hemophilia A
Acquired Hemophilia

Anti-FVIII autoantibodies share similar characteristics in acquired hemophilia A patients with and without an associated disease.

Abstract presented at: 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA.
Introduction and Purpose

• Associated pathologies observed in \( \approx 50\% \) of patients with acquired hemophilia (AH)

• Aim of study: clarify relationship between an underlying disease, bleeding tendency, characteristics of anti-FVIII autoantibodies, and patient immunologic profile
Patients and Methods

• 15 patients (6 with underlying disease, 9 without)
• Median patient age 71y
• Patients classified according to bleeding tendency
• Domain specificity of anti-FVIII autoantibodies analyzed in ELISA
• 14/15 patients received rFVIIa, aPCC, or porcine FVIII
• All received immunosuppression
• 14/15 patients achieved initial complete remission; 6 patients relapsed
Characteristics of Anti-FVIII Autoantibodies

• Similar in patients with or without underlying disease
  – Primarily targeted the FVIII light chain (LC), with dominance of epitopes located on C2 domain
  – Belonged to subclasses IgG1, IgG2, IgG4
  – No correlation between subclass levels and total amount of anti-FVIII antibodies or inhibitory anti-FVIII antibodies
  – IgG subclass levels did not correlate with bleeding tendency
  – Lower levels of FVIII activity observed in disease-associated patients (median FVIII:C 0.5%) compared to patients with idiopathic AH (FVIII:C 1.5%), but difference not statistically significant
  – FVIII:C levels and inhibitor titers at clinical presentation did not correlate with bleed severity
## Characteristics of Anti-FVIII Autoantibodies (cont)

<table>
<thead>
<tr>
<th>Bleeding Phenotype</th>
<th>FVIII:C Levels</th>
<th>FVIII Inhibitor Titer Median (range) (BU/mL)</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>1.2% (1% – 6%)</td>
<td>35 (29 – 55)</td>
</tr>
<tr>
<td>Moderate</td>
<td>3.6% (0% – 6%)</td>
<td>49.5 (9 – 156)</td>
</tr>
<tr>
<td>Severe</td>
<td>0.5% (0% – 10%)</td>
<td>173 (2.2 – 614)</td>
</tr>
</tbody>
</table>
Conclusion

- These results challenge the conclusions of other small cohorts that suggest different immunologic profiles exist between disease-associated and idiopathic AH
Hemophilia B

Burden of bleeding episodes among persons with hemophilia B.

Poster presented at: 65th Annual Meeting of the National Hemophilia Foundation; October 3-5, 2013; Anaheim, CA.
• Study purpose
  – Characterize burden of bleeding in patients with hemophilia B
    • An often underrepresented group in population-based and health services surveillance
  – Assess relationship between HRQoL and bleeding frequency in hemophilia B population
Methods

• Prospective data collection
  – Bleeding episodes
  – Healthcare utilization
  – Burden of illness
• 10 HTCs in 11 states
• Initial patient interview and 8 quarterly follow-up surveys
• N=110 participants
  – Completion of ≥3 follow-up surveys
• Analysis of baseline and 1-year follow-up
• Burden of bleeding included
  – Bleeding-related healthcare services utilization
  – Hemophilia-related absenteeism from work/school
  – Decreased patient-reported HRQoL
Results

• **Patient characteristics**
  – 110 subjects (55 children, 55 adults)
  – Severe hemophilia B: children 49%, adults 44%
  – Prophylaxis (severe only): children 63%, adults 50%

• **83 (75%) participants reported having at least 1 bleeding episode during study period**
  – Participants with severe hemophilia on prophylaxis had significantly ($P = .0428$) fewer bleeding episodes compared to those on episodic therapy
Results (cont)

- Significantly fewer clinic visits and less time in telephone contact with HTC staff were observed among patients with less bleeding frequency.
- Mean absenteeism from work/school due to hemophilia ranged from $1.6 \pm 4.9$ to $6.0 \pm 10.6$ days among bleeding frequency subgroups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>ABR 0-1 (N=49)</th>
<th>ABR 2-5 (N=31)</th>
<th>ABR 6-10 (N=11)</th>
<th>ABR 11-20 (N=15)</th>
<th>ABR &gt;20 (N=4)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER visit</td>
<td>0.1±0.4</td>
<td>0.3±0.6</td>
<td>0.4±0.9</td>
<td>0.1±0.3</td>
<td>0</td>
<td>0.4416</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>0.3±0.6</td>
<td>1.0±1.9</td>
<td>6.4±17.3</td>
<td>1.21±1.5</td>
<td>3.5±7.0</td>
<td>0.0426</td>
</tr>
<tr>
<td>Time on phone with HTC staff (mins)</td>
<td>32.6±35.6</td>
<td>86.9±66.5</td>
<td>148.3±158.2</td>
<td>135.8±144.7</td>
<td>93.0±82.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Missed days from work/school</td>
<td>1.6±4.9</td>
<td>5.0±5.4</td>
<td>6.0±10.6</td>
<td>4.2±4.2</td>
<td>2.5±4.5</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

ABR, annual bleeding rate.
• In adults, significantly higher physical component scores were reported in lower bleeding frequency subgroups.

• Physical functioning scores also decreased significantly among children as bleeding frequency increased ($P<.0001$).

• In contrast to adults, children on episodic therapy reported higher physical functioning scores from children on prophylactic therapy.
Conclusions

• Patients with hemophilia B experience increased healthcare utilization, increased absenteeism from work/school, and impaired HRQoL as a result of bleeding
• While prophylaxis can significantly reduce bleeding frequency, a significant number of bleeds were still reported by patients on this treatment
• Children on prophylactic therapy reported worse physical functioning than those on episodic therapy
Clinical Application

• Management of bleeding imposes considerable burden on providers and patients
• The finding that children on prophylaxis reported worse physical functioning than those on episodic therapy is somewhat surprising
• Future studies need to address the causal relationship between prescription of prophylaxis and patient-reported outcomes
Treatment Strategies
Earnshaw SR, McDade CL, Graham CN, Spears JB, Kessler CM.

Economic comparison of treating hemophilia patients who have developed inhibitors via immune tolerance induction versus prophylaxis and on-demand treatment with bypassing agents.

Abstract presented at: 55th ASH Annual Meeting and Exposition; December 7-10, 2013; New Orleans, LA.
Inhibitor development is the most serious complication of hemophilia

- Inhibitors substantially increase treatment costs
- Cost-effective treatment strategy is useful

3 treatment approaches for inhibitor patients

- On-demand bypassing therapy (aPCC or rFVIIa)
- Prophylactic bypassing therapy
- Immune tolerance induction (ITI) with FVIII concentrate for inhibitor eradication
Study Purpose and Methods

- Decision-analytic model developed to compare commonly used treatment regimens for patients with severe hemophilia A and inhibitors
- Compared costs and outcomes of treatment regimens throughout patient’s lifetime
- Goal to assist hemophilia providers in making more informed treatment decisions
Results

- ITI successful ~74% of the time
- Differences in costs and outcomes for 3 treatment regimens

<table>
<thead>
<tr>
<th></th>
<th>ITI Approach</th>
<th>On-demand Approach</th>
<th>Prophylaxis Approach</th>
</tr>
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<tbody>
<tr>
<td>Estimated lifetime treatment costs</td>
<td>$22,201,832</td>
<td>$38,656,756</td>
<td>$42,104,865</td>
</tr>
<tr>
<td>(USD)</td>
<td></td>
<td></td>
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<tr>
<td>Projected Patient Lifespan</td>
<td>74.3y</td>
<td>69.6y</td>
<td>69.6y</td>
</tr>
<tr>
<td>Discounted quality-adjusted life years*</td>
<td>25.1y</td>
<td>14.7y</td>
<td>20.5y</td>
</tr>
<tr>
<td>Number of bleeding events</td>
<td>801</td>
<td>1819</td>
<td>694</td>
</tr>
</tbody>
</table>

*Year of life adjusted for its quality or its value.
Conclusions

• For those with inhibitors, ITI results in lower lifetime costs and a greater number of life years and quality-adjusted life years compared to on-demand and prophylactic treatment approaches
Clinical Application

- Economic burden of inhibitor antibodies is enormous
- Although associated with high initial costs, if successful, ITI may be cost-effective over the long term
- Development of improved methods of ITI and more effective treatment for bleeds remain high priorities for the inhibitor population
Shapiro AD, Neufeld EJ, Blanchette V, Salaj P, Gut RZ, Cooper DL.

Safety of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors: overall rFVIIa exposure and intervals following high (>240 µg kg\(^{-1}\)) rFVIIa doses across clinical trials and registries.

**Background and Study Purpose**

- Indicated dosing of rFVIIa for treatment of bleeds in congenital hemophilia with inhibitors (CHwI) is 90 µg/kg q2-3h in US or a single 270 µg/kg dose in European Union
  - ~90% reported efficacy for both regimens
- **Study Purpose: Methods**
  - Post hoc assessment of the safety and use of rFVIIa in CHwI and the impact of >240 µg/kg on the dosing interval and frequency of subsequent bypassing therapy
  - Data sources included US and global clinical trials and registries incorporating active safety monitoring
  - Analysis of >60,000 rFVIIa doses used in the on-demand and prophylactic treatment of pediatric and adult patients
• 481 patients with CHwI used rFVIIa on-demand or prophylactically
  – 3947 total bleeds and 43,135 prophylaxis days
• Dose exposure
  – 61,734 recorded rFVIIa doses
    • 11,021 in adult patients; 50,713 in pediatric patients
  – Of the total doses recorded, 52% exceeded 120 µg/kg; 37% exceeded 160 µg/kg; and 15% exceeded 240 µg/kg
  – 24,352 doses used for on-demand treatment of acute bleeds
    • 53% were in range of 80-120 µg/kg; 42% exceeded 120 µg/kg; 27% exceeded 160 µg/kg; 8% exceeded 240 µg/kg
  – Prophylactic rFVIIa dosing
    • 34% were in range of 80-120 µg/kg; 59% exceeded 120 µg/kg; 44% exceeded 160 µg/kg; and 20% exceeded 240 µg/kg

*No arterial or venous thromboembolic events reported in any patient receiving on-demand or prophylactic rFVIIa.
Conclusions

- These data support the safety of rFVIIa within the CHwI patient population
- Substitution of fewer high doses of rFVIIa for more frequent lower doses may alleviate the need for short-interval repetitive dosing, improve treatment adherence, and potentially produce a faster treatment response
Clinical Application

• Clinical use of and response to bypassing agents in CHW1 is more heterogeneous than standard factor replacement therapy
• Optimal use and dosing interval for treatment of bleeding with rFVIIa varies among individual patients and bleeding episodes, and is often determined empirically over time
• Due to clinical heterogeneity and small patient numbers, studies to more precisely define optimal dosing are unlikely
Antunes SV, Tangada S, Stasyshyn O, et al.

Randomized comparison of prophylaxis and on-demand regimens with FEIBA NF in the treatment of haemophilia A and B with inhibitors.

Introduction and Study Purpose

- Reports in the medical literature have demonstrated that prophylaxis with bypassing agents reduces morbidity and improves general health and QoL in patients with hemophilia
  - Most recently, the Pro-FEIBA study demonstrated a statistically significant reduction in bleeding episodes, hemarthrosis, and target joints in hemophilia patients with high-titer inhibitors who received aPCC prophylaxis over a 6-month period (Leissinger C, et al. *N Engl J Med*. 2011;365:1684-1692)

- Present study designed to compare the efficacy, safety, and HRQoL of prophylactic regimen of aPCC and on-demand regimen over a 12-month observation period
  - Phase 3, randomized, multicenter, open-label, 2-arm parallel study
  - Primary outcome: reduction in annualized bleeding rate (ABR) among subjects on prophylaxis compared to subjects treated on-demand over 12-month period (±14 d)
  - Prophylaxis dosing was 85±15 U/kg by IV bolus infusion every other day
Results

• 36 subjects randomized and treated with aPCC
  – Hemophilia A or B and either high-titer inhibitor or low-titer inhibitor refractory to FVIII or FIX treatment
  – 17 in prophylaxis arm; 19 in on-demand arm

• During 12-month study period, 196 bleeding episodes occurred during prophylaxis; 629 occurred during on-demand treatment

• Occurrence of new target joints was substantially lower in prophylaxis arm compared to on-demand arm
  – On-demand: 23 new target joints in 11/19 (57.9%) subjects
  – Prophylaxis: 7 new target joints in 5/17 (29.4%) subjects
• The majority of bleeding episodes occurred in joints
  – 572/629 (91%) during on-demand
  – 171/196 (87%) during prophylaxis

• For new target joints, median [interquartile range (IQR)] ABR was significantly lower in the on-demand arm (5.9 [12.9]) than in the prophylaxis arm (0 [4.1])
  – Suggests longer duration of prophylaxis may further reduce bleeding in some patients

• Median [IQR] total aPCC usage to treat bleeding episodes was significantly higher during on-demand therapy (4049.7 [5083.9] U/kg) than during prophylactic therapy (1524.9 [2590.2] U/kg)
• NO thromboembolic events or major safety issues reported for any of the 36 subjects

• Study was not powered to show statistically significant differences in QoL
  – Greater tendency for improvement was noted in prophylaxis arm with respect to:
    • Haem-A-QoL total score
    • Scores for 8/10 Haem-A-QoL domains
    • General pain scores
    • Number of days lost from work or school due to bleeding episodes
Conclusions

• Prophylaxis with aPCC shown to be safe and effective in reducing:
  – Bleeding episodes
  – Bleeding into all joints including target joints
  – Development of new target joints in patients with persistent high-titer inhibitors and low-titer inhibitors refractory to FVIII or FIX treatment
Clinical Application

• This study adds to the growing body of evidence that supports the use of prophylaxis with bypassing agents for hemophilia patients with inhibitors
Thank You

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