Out of Control:  
What Sends an Inhibitor into Overdrive?

Sue Geraghty, RN, MBA 
Retired Nurse Coordinator 
University of Colorado Denver HTC 
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What We Know

- Inhibitors occur in approximately 30% of factor VIII patients and 1-3% in factor IX
- Usually, but not always, occur in severe patients, <1% clotting factor
- According to ISTH a Bethesda Unit of 5 differentiates between low and high responding inhibitors
- Usually occurs within the first 50 exposure days, median 9-12 [Hay, 2006]
- Genetic factors and environmental factors

Genetic Factors:  
What We Cannot Change

Genetic Mutation
Race/ethnicity
Family History
No single genetic factor is responsible for inhibitor development

Developed by Sue Geraghty, R.N.
Genetic Mutations

- Large gene deletions
  - Inhibitors occur in 88% of patients when multiple domains are involved
- Nonsense mutations
- Intron 22 (Inversion 22)
  - Most common mutation in severe hemophilia A
  - 21% incidence of inhibitor development (Oldenberg, et al 2004)

Race/ Ethnicity

- African Americans
- Hispanics
- Mechanism for these differences is unclear

Family History

- Some studies show inhibitor development is more likely if there is a family history
- Brother pairs, both don’t always have inhibitors
- Immune response traits
Non Genetic/Environmental Factors
Can These Be Changed?

Age at First Exposure

- Not predictable
- Family history vs. no family history
  - Circumcision
- Rivard study
  - Postpone use of factor VIII until age 2
  - 11 patients enrolled
  - Used rVIIa
  - 3/11 were able to postpone treatment

Intensity of First Exposure

- Significant cell injury or inflammation considered a danger signal
  - Stimulates antigen presenting cells amplifying immune response
- No control over when major bleeding episodes occur
- Delay major surgeries if possible
- Not a reason to withhold treatment
  - Monitor more closely
Prophylaxis

- 2 studies report a decrease risk of inhibitor development in patients receiving prophylaxis vs. on demand treatment
  - Italian study by Santagostino
  - CANAL (concerted action on neutralizing antibodies in severe hemophilia A)
- Need for prospective studies

Type of Product

- Recombinant vs. Plasma derived concentrate with and without vW factor
- Conflicting reports
- Ongoing research
  - SIPPET (Survey of Inhibitors in Plasma Product Exposed Toddlers)
    - PUP study comparing 2 types of products

European Haemophilia Treatment Standardization Board (EHTSB)

- Review of literature and survey of members
- Desirable to minimize intensive treatment whenever possible
- Offer prophylaxis to all children
  - Optimal frequency and dose still to be determined
- Vaccinations should be given sub-q and concomitant factor avoided
- Immune challenges like infection could increase risk of inhibitor development
Why Talk About These Things?

• True— we know you or your child had or has an inhibitor
• Do we care why you got the inhibitor?
  — Yes
• Do these non-genetic or environmental risks continue to play a role in...
  — Outcomes
  — Treatment

When Might an Inhibitor Go Into Overdrive

• No data to support this information at this time
• Area in need of research
• Areas of concern
  — Surgery or intensive therapy
  — Infection
  — Vaccination
  — Puberty
  — Change in treatment
  • Either product or frequency

Surgery or Intensive Therapy

• A sudden increase in the amount of factor infused
  — May trigger an immune response
• Danger Signals
  — Cell injury
  — Inflammation
Infections

- Frequent use of ports and lines in patients who already have an inhibitor
- Repeated assaults on the immune system
- Post surgical infection
  - Lesser degree

Vaccinations

- Inconclusive data
  - Area for research
- "Revs" up the immune system
  - Opportunity for the inhibitor to become stimulated

Pre-puberty/Puberty

- Anecdotal to date
- Change in hormone levels
  - Possible trigger
  - Unknown at this time
Changes in Therapy

- Changing products
  - Recombinant to plasma derived with vW factor
  - Changing between different recombinant products
- Change in frequency of infusion
  - Stopping immune tolerance
  - Reintroduction of factor

Case Study 1

- Diagnosed shortly after birth with severe hemophilia A
- Inhibitor developed at 9 months of age, high titer
- Successful ITT, but continued to require 50 units/kg every other day
- Age 9 switched recombinant products in order to transition to peripheral infusion
- Inhibitor returned, higher than it was prior to tolerance
- 4 years later despite aggressive treatment and immune modulation the inhibitor persists
  - Multiple hospitalizations
  - Decreased QOL for patient and his family

Case Study 2

- No family history of hemophilia, diagnosed following circumcision with severe hemophilia A
- Developed high titer inhibitor around age 2
- Underwent successful ITI and was on maintenance/prophylaxis
- Beginning in middle school, patient refused infusions. MDC stated if he infused once every 2 weeks that was good
- Multiple left knee bleeds, failed synovectomy
- Age 18, infusing about once every 3-4 weeks patient underwent a left total knee replacement
- Inhibitor did not return
Age and It’s Role

- According to a study by Dr. Charles Hay, 73% of inhibitors develop in the 1st decade of life
- There is a second cluster that occurs in the 6th decade of life
  - These patients have received hundreds of factor infusions
  - Usually arise after intensive therapy following a bleed or a surgical procedure

Keith Hoots, MD Call for Research in 2006

- Focus on the 20% of inhibitors that are not eradicated by ITT
- 4 areas to consider
  - Do clotting factor have differential immunogenicity
  - Studies to examine quantitative and qualitative effects of clotting factors and the interaction with vaccination and infection
  - Will concurrent immune suppressive strategies enhance inhibitor eradication
  - Are there new treatments to reduce the frequency and severity of acute hemorrhage in these patients

In Response

- Trial using recombinant porcine factor VIII, OBI-1
- Pro-Feiba, Feiba prophylaxis
- Factor VIIa prophylaxis
- SIPPET
- Other areas of research
In Conclusion

- We don’t know definitively what causes inhibitors
- We don’t know why some but not all inhibitor patients tolerate
- Lastly we do not know what sends an inhibitor into overdrive
- More questions that answers

Individuals

They are all dogs but are all different
What works for one person may not work for another

Thank You

Questions??