MISSION

The Hemophilia Federation of America (HFA) is a national nonprofit organization that assists and advocates for the bleeding disorders community.

Hemophilia A and Inhibitors: A Journey Down the Road Less Traveled

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Gateway to a STRONGER COMMUNITY

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Disclosures

- Advisory board member/consultant
  - Baxter
  - Bayer
  - CSL Behring
  - Grifols
- Research support
  - Pfizer

Outline

- Overview of inhibitors
  - Anti-factor VIII antibody testing
- Prophylaxis
- ITI
- Treatment of bleeding
  - Standard
  - New/in development

*Off label use of combination therapy with factor VIII and bypassing agents along with porcine factor VIII will be discussed.

Inhibitor Development

Inhibitors are the most significant complication of hemophilia in the developed world

Major questions

- Can we predict who will get inhibitors and can that development be prevented?
- How can we eradicate inhibitors?
- **How do we treat bleeding in patients with inhibitors?**

What are Inhibitors?

- Antibody
  - Protein used by the immune system to identify and neutralize foreign objects such as bacteria and viruses.
  - The **antibody** recognizes a unique part of the foreign target, called an antigen
  - Some antibodies to fVIII inhibit the function of fVIII i.e. "Inhibitors"
- Frequency
  - Severe hemophilia A 20-30%
  - Mild & moderate hemophilia A 3%-13%
  - Acquired hemophilia ~1.4 per million

How Do We Know that a Patient Has an Inhibitor?

- Bleeding is not controlled or prevented as expected
- Routine screening
- Bethesda assay
  - Titer: the dilution of plasma that gives 50% residual fVIII activity when mixed with normal pooled plasma
  - Measured in Bethesda units per mL plasma(BU/ml)
  - <5 BU/ml considered low titer
  - >5 BU/ml considered high titer

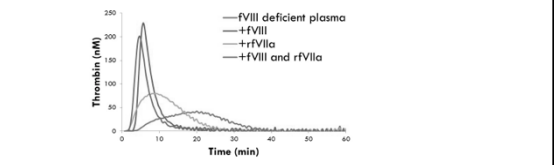
Why does my doctor say every patient with hemophilia A and an inhibitor is different?

Clinical Scenarios

- 58 year old with moderate Hem A (1.7%) who is clinically responsive to treatment with fVIII and has an inhibitor titer of 22 BU/ml.
- 18 month old with severe Hem A (<1%) with good clinical response to high dose fVIII despite inhibitor titer of 32 BU/ml and poor fVIII recovery. Poor response to bypassing agents.
- 18 mo with inhibitor titer of 75 BU/ml on ITI able to stop bypassing agent prophylaxis because no longer bleeding
- 15 yo with inhibitor titer of 8 BU/ml who is bleeding despite bypassing agent therapy and has failed ITI x 2 (4.5 years total therapy)

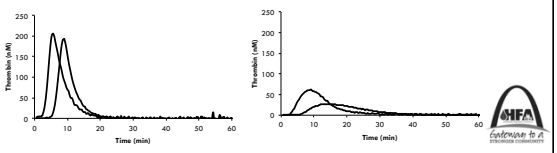
Why does my doctor say every patient with hemophilia A and an inhibitor is different?

2 Very Different Inhibitor Patients

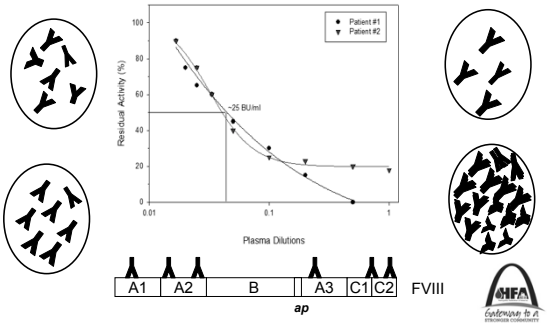


IB001A: 22 BU/ml

IB008H: 29 BU/ml



Same Titer but Very Different Inhibitors



My doctor always said prophylaxis was important does that change now that I have an inhibitor?

US Expert Panel Recommendations

- Prophylaxis should be considered optimal therapy for severe hemophilia
  - Keep level above 1% between doses
- Institute prophylaxis by age 1 to 2
- Joint status; bleeding and costs should be documented carefully
- Consider prophylaxis for other age groups with careful cost-benefit analysis

MASAC #193

Prophylaxis in Hemophilia With Inhibitors

FEIBA

- Randomized, prospective, cross-over design
- 85 U/kg 3 non-consecutive days per week
- Both total bleeds and joint bleeds reduced

rFVIIa 90 vs 270 mcg/kg/day

- Randomized, prospective
- Similar decreased in bleeds in both prophylaxis groups

Leissenger et al. N Engl J Med. 2011.
Konkle et al. *J Thromb Haemost* 2007.

How am I going to stop bleeding now that I have an inhibitor?

Treatment of Acute Bleeding

- Management strategies based on 2 inhibitor characteristics: titer and responder status
  - High-titer/high-responding:
    - >5 BU/ml- at any time
    - 50% to 75% of all inhibitors
  - Low-titer/low-responding:
    - <5 BU/ml
    - No increase in titer with continued fVIII exposure
    - 25% to 50% of all inhibitors

Treatment of Bleeding

- No therapy currently available works as well as fVIII!

Currently Available:

- Bypassing agents
  - Recombinant factor VIIa (rFVIIa, NovoSeven)
  - Activated prothrombin complex concentrates (aPCC, FEIBA)
- High-dose fVIII
- Recombinant porcine fVIII

Treatment based on Inhibitor Titers

Low titer: <5 BU/ml

- Maybe overcome with higher doses of fVIII

High titer: >5 BU/ml

- Classically thought not likely to be overcome with higher doses of fVIII
- Bypassing agents

Porcine FVIII

- Recombinant porcine fVIII
  - NOTHING WORKS AS WELL AS FVIII!!
  - Previous plasma derived porcine fVIII pulled from the market ~10 years ago
  - Cross-reactivity ~10% to anti-human fVIII inhibitors
  - Risk of also developing anti-porcine fVIII inhibitors
  - Currently approved for patients with acquired hemophilia

Bypassing Therapy for Treatment of Bleeds - aPCCs

Pros
- Half-life 8-12 hours
- 1-2 x per day dosing adequate for most bleeding
- 3x per week for prophylaxis

Cons
- Large volume
- Plasma product

Bypassing Therapy for Treatment of Bleeds - rFVIIa

Pros
- Small volume
- Recombinant

Cons
- Half-life 2-4 hours
- Every 2-4 hour dosing for major bleeds
- Daily for prophylaxis

2 Bypassing Agents: Which Is Better?

- ~80% efficacy for bleeding events
- FENOC study
  - Prospective randomized crossover study of aPCC compared to rfVIIa to treat joint bleeds
  - Primary endpoint control of bleeding at 6 hrs
  - Results showed similar efficacy
  - *More discordance than anticipated indicating individual variability in response to bypassing agents*

Astermark J, Donfield SM, DiMichele DM et al. Blood 2007;109:546-551.

ITI seems really tough….Is it really worth it and if so how do I know which regimen to use?

Short Term vs Long Term Outlook

- Cost analysis
  - ITI followed by treatment with fVIII less expensive than lifetime of bypassing therapy
- Advantages of treatment
  - If successful less life bleeding and better quality of life.
- Disadvantages
  - High cost/effort and patient may ultimately fail

Earnshaw et al. Haemophilia. 2015.

ITI Options

- Recombinant vs. plasma derived fVIII
- Low dose vs high dose
- Access: peripheral vs central venous line

It's been a couple of years since I started ITI and I still have my inhibitor are there other options?

What about ITI with the new longer acting fVIII products?

Immunosuppressive Agents

- Rituximab (anti-CD20)
  - Monoclonal Ab that recognizes CD20 a marker on B cells (ultimately become antibody secreting cells)
- Other less specific immunosuppressive agents: Cyclophosphamide, mycophenylate, rapamycin
- Usually with concomitant ITI

Longer Acting FVIII Products and ITI

- No data just hypotheses
- All products are different
- Only data available is in PTPs without history of inhibitors

What new research may help patients with hemophilia and inhibitors?

*Caveat: new isn't always better

New Agents in Development

- Longer half-life rfVIIa
  - 2 trials stopped because of antibody development
- Inhibitors of the natural anticoagulants
  - 1 trial stopped because of increased bleeding
- Bispecific antibody to factor IXa and factor X

Questions???

Anti-FVIII Antibodies 201

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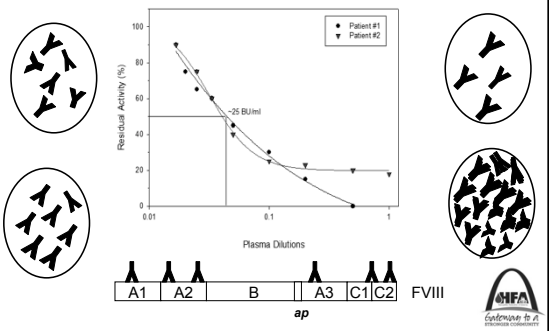

Taking a Step Back to the Research Lab

- Mouse model of hemophilia A
- >100 purified monoclonal antibodies to fVIII
- Allowed us to ask questions:
  - How different are antibodies to different epitopes of fVIII?
  - Does inhibitor titer correlate with bleeding symptoms?
  - Does antibody epitope influence response to treatment with fVIII?

Different Types of Anti-FVIII Abs

- High titer, fast onset of action, inhibit fVIII completely
- High titer, slow onset of action, inhibit fVIII completely
- High titer, fast onset of action, do NOT inhibit fVIII completely
- Low titer, fast onset of action, inhibit fVIII completely
- Low titer, fast onset of action, do not inhibit fVIII incompletely
- No inhibition of fVIII

Challenges in Patient Plasma

- Most patients have more than one type of antibody
- Currently unable to separate into individual antibodies
- Must rely on the final answer of all of the antibodies
- Distribution and type of antibodies change over time

Clinical Scenarios

•58 year old with moderate Hem A (1.7%) who is clinically responsive to treatment with fVIII and has an inhibitor titer of 22 BU/ml.

- High titer, fast onset of action, does NOT completely inactivate fVIII
- 35% of infused fVIII activity remains after inhibitor is allowed time to inhibit as much as possible
- Decreased recovery but normal half-life

Clinical Scenarios

•18 month old with severe Hem A (<1%) with good clinical response to high dose fVIII despite inhibitor titer of 32 BU/ml and poor fVIII recovery. Poor response to bypassing agents.

- High titer with slow onset of inhibition
- Takes almost 2 hours to completely inhibit fVIII in the lab

Clinical Scenarios

•15 yo with inhibitor titer 8-300 BU/ml who is bleeding despite bypassing agent therapy and has failed ITI x 2 (4.5 years total therapy)

- Inhibits fVIII rapidly and completely
- Restarted ITI with Rituximab
  - Now low titer x 2.5 years with no use of bypassing agents
  - Infuses fVIII 75-100 U/kg/d with levels >1% for 12 hours
  - Second dose in evening if major activity

Clinical Scenarios

•18 mo with inhibitor titer of 25-75 BU/ml able to stop bypassing agent prophylaxis because no longer bleeding

- Very rapid inhibition of fVIII
- Residual activity of 6% remains from 15 minutes past 120 minutes
- Bypassing agents used for laceration to the forehead and CVL placement

Conclusions

- Inhibitors are the most significant problem in hemophilia A patients in the developed world.
- Better treatment options are needed.
- Improved abilities to define individual patient characteristics may help in choosing treatment strategies and predicting response.

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Thank You!

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