

What's New With ITI?

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Eradication of Inhibitors

- Immune tolerance induction (ITI) or immune tolerance therapy (ITT)
- Immunosuppression
- Malmo regimen
- Plasmapheresis/immunoadsorption
- Rituximab

ITT

- What is it?
 - Providing factor on a regular (often daily) basis in order to “teach” the immune system that it should not make antibodies against this protein
 - Immunologically similar to desensitization therapy (for bee stings, medications, etc.)

ITT

- Questions remaining
 - When should you start with respect to
 - Age
 - Inhibitor titer
 - What is the best regimen?
 - Which type of concentrate should be used?
 - How long to treat?
 - When can you stop?
 - What should you do when you stop?

ITT

- When to start?
 - Age
 - Younger age patients respond better
 - Inhibitor titer
 - Lower titer at start of ITT respond better
 - Lower historical peak titer respond better
- My advice
 - If titer is not high (<10), start right away
 - If titer is high, wait until titer is lower and avoid products which contain factor VIII (or IX)... but don't wait too long

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ITT

- What is the best regimen?
 - Not known
 - Current, international study under way (for FVIII deficiency) comparing 50 units/kg every other day with 100 units/kg daily
 - Some studies suggest higher daily doses (100-200 units/kg are more effective)
 - Others show that a lower dose (25-50 units/kg) every other day is equally effective
- My advice
 - Start with high daily dose (100 units/kg daily or twice a day)
 - If response is good, consider lowering the dose

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ITT

- Which type of concentrate should be used?
 - Standard is to use recombinant factor VIII
 - Emerging data suggests that a concentrate with von Willebrand factor in it may be able to salvage patients who failed recombinant factor VIII
 - Germans suggest using these factors up front
 - Downside is that von Willebrand factor products are plasma derived
 - Answers unknown

ITT

- My advice
 - Use recombinant factor VIII
 - If immune tolerance is not achieved, consider trying a von Willebrand factor–containing product (Humate-P, Alphanate SD, or Koate DVI)

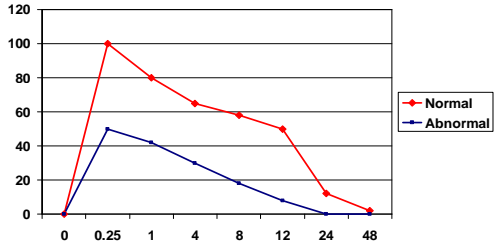
ITT

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ITT

- How long to treat? When can you stop?
 - Unknown
 - Until inhibitor is eradicated
 - Bethesda titer of 0
 - Normal pharmacokinetic (survival) study
- My advice
 - Until you get a normal survival study
 - Can consider lowering dose to “prophylactic mode” if titer is undetectable even with abnormal survival

Pharmacokinetic Study



ITT

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ITT

- What should you do when you stop?
 - Switch to prophylaxis mode
 - This will ensure continued exposure to the factor to prevent recurrence of inhibitor and of course help prevent bleeding episodes
- My advice
 - As above



Eradication of Inhibitors

- ITT
- Immunosuppression
- Malmo regimen
- Plasmapheresis/immunoadsorption
- Rituximab



Immunosuppression

- Various medications have been tried, but in general, these have not been successful in congenital hemophilia
 - Steroids, cyclophosphamide, cyclosporine, and others
- Immunosuppression is effective in acquired hemophilia
- Rituximab will be discussed separately
- My Advice
 - I would not treat with "standard" immunosuppressive drugs



Eradication of Inhibitors

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Malmö Regimen

- Combination of ITT with factor and immunosuppressive medications
- It has been suggested that inhibitors are eradicated more rapidly with this method
- Side effects of medications and success of standard ITT has led few outside of Scandinavia to use this regimen
- My advice
 - Use standard ITT



Eradication of Inhibitors

- ITT
- Immunosuppression
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- Plasmapheresis/immunoabsorption
- Rituximab



Plasmapheresis/ Immunoabsorption

- This is an effective way to immediately reduce the inhibitor titer; however, it does not have a lasting effect
- Useful in situations of severe bleeding in order to reduce inhibitor titer to allow use of standard factor replacement
 - Used only if bypass therapy fails

Eradication of Inhibitors

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Rituximab

- Relatively new medication which targets CD20+ cells (B cells), which are the cells that make antibody
- Approved by the US FDA for treating B-cell lymphoma
- Now also being used to treat a variety of autoimmune diseases

Rituximab

- There are a few reported cases of success in hemophilia patients with inhibitors



Rituximab

- It is important to understand that inhibitors in congenital hemophilia are different than autoantibodies in autoimmune disease
 - In congenital hemophilia, these are “naturally” occurring antibodies, whereas in autoimmune disease, they are pathologic
- It is much harder to eradicate a natural immunity
- Although rituximab is effective in autoimmune disease, it is not necessarily going to be effective in congenital hemophilia with inhibitors



Rituximab

- Potential side effects
 - Rituximab has been to shown to be quite safe despite its major effect on the immune system
 - However, there are reports of serious opportunistic infections in patients who have received it
 - Hepatitis B
 - Progressive multifocal leukoencephalopathy (PML)



Rituximab

- A clinical trial is under way
- My advice
 - Rituximab should be reserved for patients in whom multiple attempts with various approaches for immune tolerance have failed and the patient is having significant bleeding problems
 - OR
 - In the setting of a clinical trial

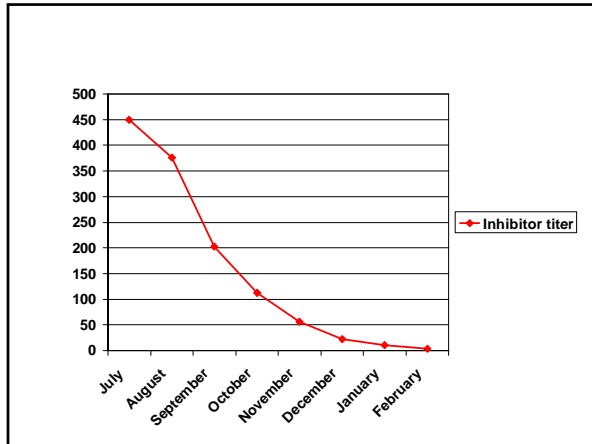
Cases

Case 1

- A 15-month-old child with severe FVIII deficiency and a history of 2 recent joint bleeds
- It was decided to start prophylaxis
- Patient was admitted for port placement
- 2 days postop, patient has a large, expanding hematoma over new port
- Despite standard factor replacement therapy, the hematoma worsens

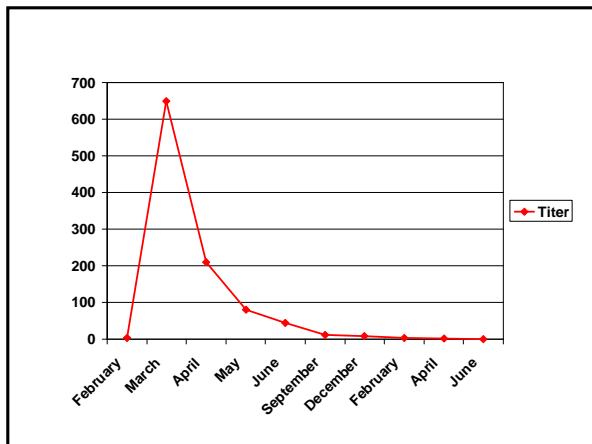
Case 1

- An inhibitor is measured and the titer is 450 BU
- The patient is treated with a bypassing agent and bleed resolves
- Due to high inhibitor titer, immune tolerance is delayed
- Inhibitor titers are measured monthly
- All products with FVIII are avoided
- Bleeds are treated with a bypassing agent



Case 1

- At a titer of 3 BU immune tolerance is started at 100 units/kg/day with recombinant factor VIII
- Inhibitor titer increases to 650 after resuming factor VIII





Case 1

- After 15 months of daily FVIII, his inhibitor titer is 0
- A pharmacokinetic study demonstrates normal survival
- The patient is switched to prophylaxis
- Currently, inhibitor is eradicated



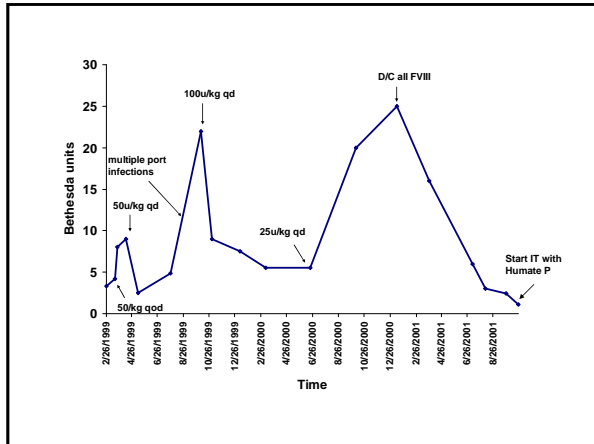
Case 1: Points

- Fairly straightforward case
- Waiting to start ITT until inhibitor titer is down is likely important
- The rise in inhibitor titer after resuming recombinant factor VIII is expected and not concerning
- This represents a successful and typical pattern of ITT



Case 2

- A 14-month-old child develops inhibitor following port placement (like case 1)
- Inhibitor titer is 4
- Patient begins ITT at 50 units/kg every other day with recombinant factor VIII

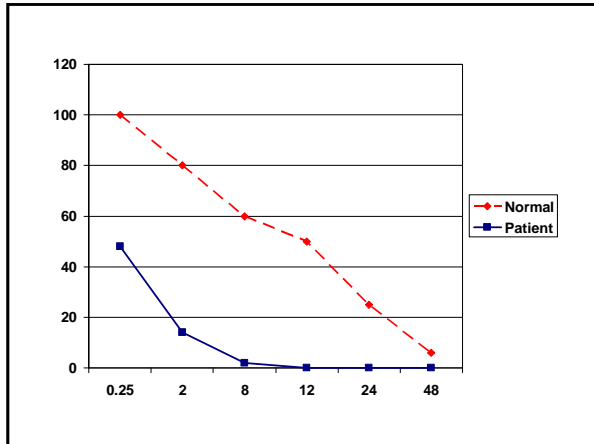


Case 2

- Despite multiple attempts with various doses of recombinant factor VIII, the patient's inhibitor titer remains elevated
- It is decided to avoid all FVIII products
- Inhibitor titer drops to 1.1 and ITT is resumed with Humate-P, a von Willebrand factor-containing FVIII product

Case 2

- After 1 year of Humate-P at 100 units/kg twice a day, the dose is reduced to once a day
- The inhibitor titer drops to 3
- He maintains this dose for another 5 months, and the inhibitor drops to 0
- A pharmacokinetic study is performed



Case 2: Points

- Immune tolerance dosing is unknown; in this case, all the various doses were not effective
- Infections can raise inhibitor titer
- If ITT is not successful with recombinant factor, consideration should be given to using a von Willebrand factor-containing FVIII product such as Humate-P, Alphanate SD, or Koate DVI
