



Information for
Hemophilia A
Patients

Embarking on Immune Tolerance Induction (ITI)

This brochure has been developed as a guide to patients and their families that are considering ITI treatment to manage inhibitors to FVIII. Talk to your healthcare professional to determine the option that is right for you.

Hemophilia Overview

- Hemophilia is an inherited bleeding disorder in which a person's blood does not clot properly
- Hemophilia A is the result of a deficiency of the Factor VIII (FVIII) protein. This protein is important to stop bleeding¹
- Treatment and prevention of bleeding is achieved by replacing the deficient clotting factor
- A complication of factor replacement therapy is the development of antibodies against factor (known as inhibitors)
- In some patients, the immune system recognizes the infused factor as a foreign substance and stimulates the production of antibodies (inhibitors)²

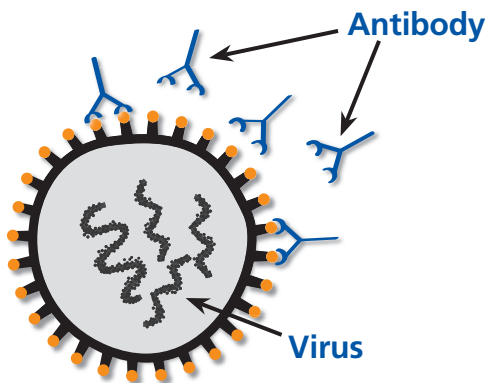
Inhibitor Overview

The Immune System

- The immune system keeps you healthy
- It is your body's defence system to protect you from diseases and germs
- It attacks and destroys any "foreign" agent which manages to get inside your body

What is an Antibody?

- The immune system has various ways of responding to a foreign substance such as bacteria or viruses
- Our bodies produce specific proteins, called antibodies, that attack “foreign” substances
- The antibody identifies the foreign substance, binds to it, and helps to eliminate it from the body

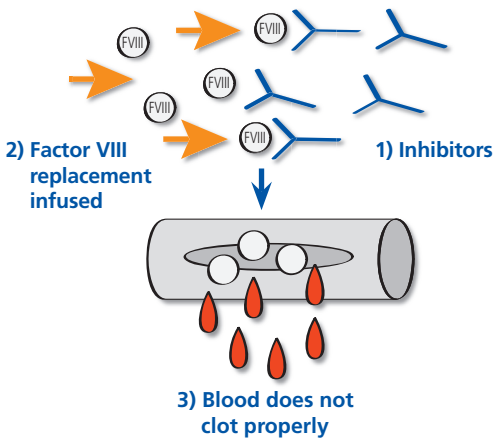


The goal of the antibody is to attack the virus and destroy it.

What are Inhibitors?

- During factor replacement therapy, some patients have an immune response to the infused factor
- An inhibitor is an antibody that develops against the infused factor
- A person who has an inhibitor will no longer respond to factor as it will be destroyed when injected into the person

Development of Inhibitors



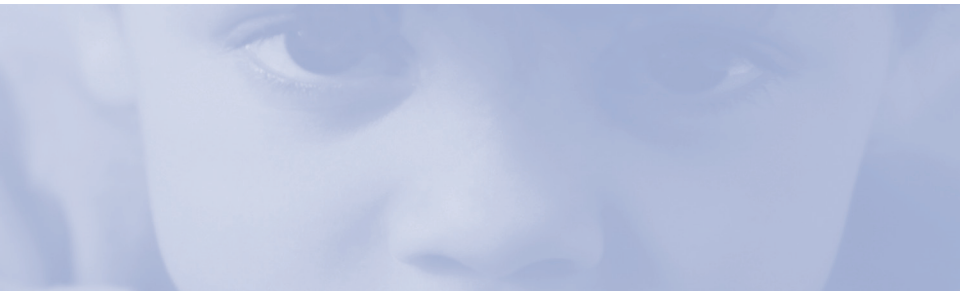
The (1) inhibitors stop the (2) infused Factor VIII from working properly causing (3) blood not to clot.

Which Patients are at Risk for Inhibitor Development?

It is not known what causes inhibitors. Risk factors that have been identified as possibly playing a role include²:

Patient-Related Risk Factors

- Race/ethnicity
- Family history of inhibitors
- Type of hemophilia genetic mutation
- Presence of other immune challenges
- Severity of hemophilia



Treatment-Related Risk Factors

- Frequency and amount of treatment
- Timing – inhibitors typically occur within the first 50 times factor is used
- Age at first exposure
- Presence of infection and/or inflammation
- Intensive exposure to FVIII
- Purity of coagulation FVIII concentrate used

Why do Inhibitors Develop?

- It is not clearly understood why some patients develop inhibitors
- It may reflect the complex interaction involved in the immune response to a foreign substance

Inhibitors can be:

- Transient (disappear on their own)
- Persistent (does not go away, even with treatment)
- Without clinical importance
- Recurring (appears again)

Detecting Inhibitors

How are Inhibitors Detected?

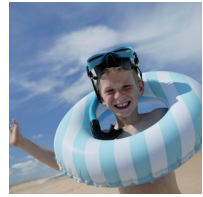
Clinical observations³

In infants and young children:

- A poor response to treatment (including prophylaxis or preventative treatment) may be seen
- High levels of inhibitors may be signalled by increased bleeding (e.g. joint bleeds)

In previously treated patients:

- An increased bleeding tendency may be seen
- There may be a high consumption of FVIII
- There may be a lack of response to Factor VIII
- Infusing FVIII does not stop the bleeding



Laboratory diagnosis

Inhibitor testing:

- The Bethesda inhibitor assay is a test used to determine the FVIII inhibitor level in your blood, which is measured in Bethesda Units or “BU”

Patients with inhibitors are categorized as high or low responders:

- Inhibitor titres or levels that are less than 5 BU/ml are considered low responders
- Inhibitor titres or levels that are 5 BU/ml or more are considered high responders

How do We Treat Patients with an Inhibitor?

There are effective treatments to eliminate inhibitors, which include the following:

■ High-dose clotting factor concentrates

For a low-responding inhibitor, patients may continue to respond to either plasma derived or recombinant factor replacement products with minimal change to their factor dose

Options for Treating Inhibitors

■ Bypassing agents

When FVIII replacement is not working, treatment of bleeding episodes requires a “bypassing” agent. This agent goes around FVIII to help the body form a normal blood clot

■ Immune tolerance induction (ITI) therapy

The goal of ITI therapy is to make your body stop producing inhibitors against the infused factor. ITI includes receiving frequent doses of factor concentrates for months or even a couple of years

Why Immune Tolerance Induction (ITI)?

- Up to 36% of individuals with severe hemophilia A develop inhibitors^{4,5}
- ITI involves repeated and persistent treatment with FVIII replacement product
- ITI is the only proven treatment known to eliminate inhibitors⁸
- The goal of ITI is to make the immune system stop making inhibitors



Choices in Clotting Factor Therapy during ITI Treatment

A choice of plasma-derived or recombinant factor VIII replacement therapy is available. It is recommended that you speak to your Hemophilia Treatment Centre to help you decide what is best for you.



Embarking on ITI Therapy

Recombinant FVIII

- Recombinant clotting factor is made in a lab by placing a human gene, that directs how to make clotting factor, into an animal cell line¹
- The cell line grows in culture to produce the factor proteins, which are then extracted and purified so that only the FVIII protein remains⁶

Plasma-Derived Factor VIII (VWF/FVIII Concentrate)

- Plasma-derived clotting factor FVIII concentrates are made from human plasma, which contains many clotting factors⁶, including Von Willebrand Factor (VWF)
- Two proposed ways that VWF can help promote immune tolerance are by: (1) blocking the inhibitor from binding to FVIII, and (2) protecting FVIII from degradation (breaking down)⁷
- To make the concentrate, the required factors FVIII and VWF are extracted from plasma, purified, then treated to inactivate any viruses that may be present⁶

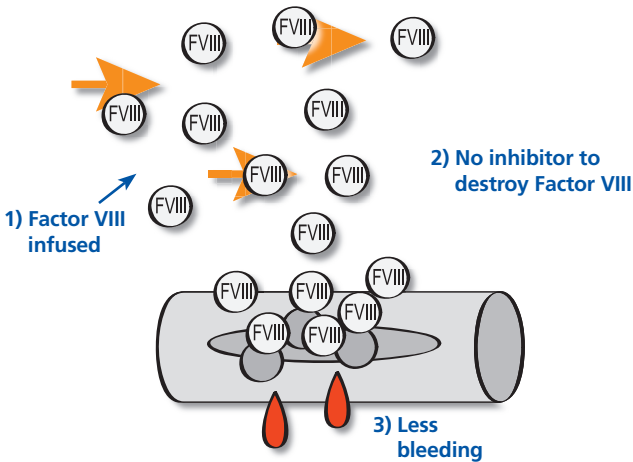


- Safety with plasma-derived clotting factor concentrates has greatly increased over the past 20 years, thanks to improvements in the screening of blood donors, testing of blood donations, factor purification techniques and, viral inactivation procedures⁶

How does Immune Tolerance Induction work?

- ITI is a successful way to “teach” the body to accept the clotting factor and reprogram the immune system so it stops producing inhibitors against the factor
- During ITI therapy, FVIII replacement product is usually given regularly (i.e. daily, three times per week) for months or even years
- Over time, regular high doses of factor concentrate help the body to accept the infused factor
- If ITI is successful, the inhibitor disappears

Embarking on ITI Therapy



How ITI helps to increase control of bleed

ITI has Become the Treatment of Choice in Order to:

- Eliminate the FVIII inhibitors
- Have FVIII treatment in case of bleeding and surgery
- Continue prophylactic treatment
- Prevent joint problems and life-threatening bleeds
- Improve quality of life
- Increase life expectancy



Tips to Help You Cope during ITI Treatment:

- Be informed
- Try to connect with other parents of children who have also had inhibitors in order to share your experiences
- Put a support system in place with family and friends
- Remember: you are not alone. Resources are available for you
- Reach out to your Hemophilia Treatment Centre and the Canadian Hemophilia Society, who can provide you with help and advice

References

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