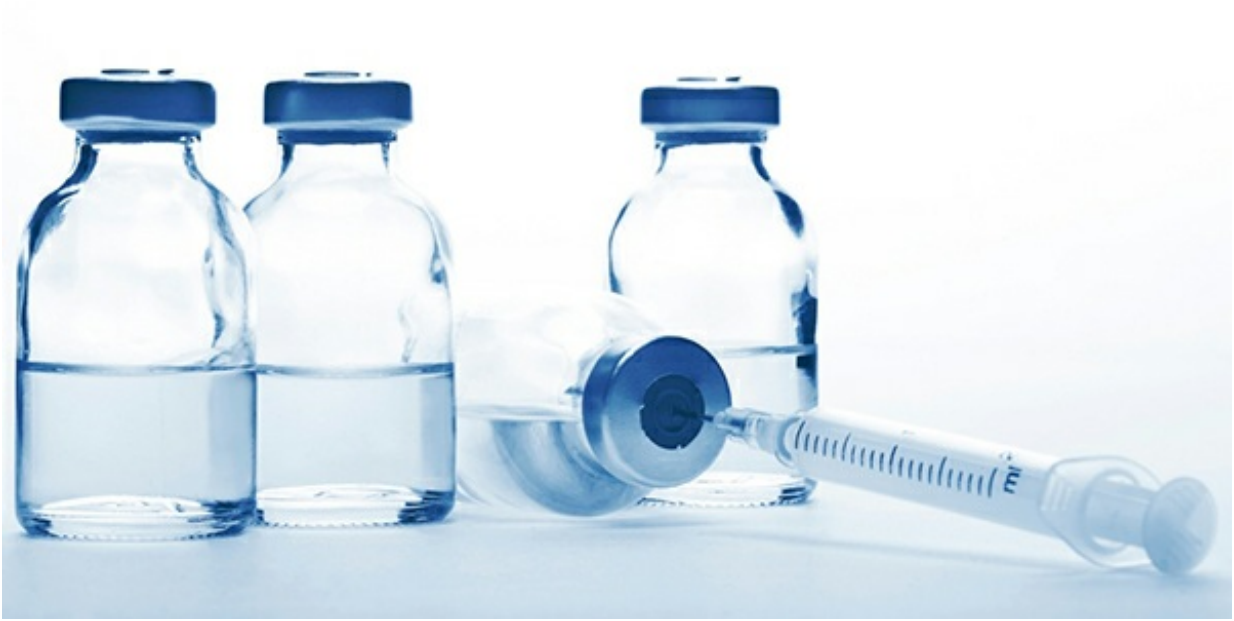
National Hemophilia Foundation

March 4, 2014



Treating a person who has inhibitors can be a challenging experience for both the patient and the healthcare team. Often, the treatment is a two-fold process. First is to manage bleeding episodes and second is dealing with the inhibitor itself. Dealing with the presence of inhibitors, can take months or even years of treatment.

Low Responding Inhibitors

For those people who have low responding inhibitor levels, continued therapy with factor replacement is often possible. This therapeutic approach provides control of both minor and more serious bleeds. To overcome the presence of inhibitors in these cases, physicians may use a greater amount of factor and might have to provide additional doses.

High Responding Inhibitors

For people with high responding inhibitors, utilizing factor is, in many cases, not possible because the inhibitor neutralizes even the largest possible dose of factor. In these cases treatment is based on the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode, physicians can remove antibodies from the body using a process called **plasmapheresis**, which lowers the level of antibodies to allow treatment with factor concentrate to treat the bleed. However, this is a temporary solution and within a few days the body will produce large amounts of new antibodies. For the person with a high responding inhibitor, most bleeding episodes are treated using bypassing products

that include **prothrombin complex concentrates (PCCs)**, **activated prothrombin complex concentrates (APCCs)** (i.e. Feiba VH, produced by Shire (formerly Baxalta) They can also be treated with a humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIIIa) by bridging activated factor IX(FIXa) and factor X(FX). A intramuscular injection taken once a week.

These bypassing products contain other factors that can stimulate the formation of a clot and stop bleeding. While these treatments are effective, they do have limitations. If they are used too often they can cause bleeding or they can generate the over-production of clots. In general, the main problems associated with bypassing products include the lack of uniform and/or universal efficacy, and at times, the development of excessive blood clotting where it is not wanted, called thrombosis. The production of clots may also be exacerbated if the person is being treated with antifibrinolytic drugs. Also, some bypassing agents contain small amounts of the deficient clotting factor, which can stimulate the continued production of more inhibitors, not allowing the inhibitor level to fall over time. Some of these bypassing products are manufactured from human plasma and are therefore at risk, although very small, of HIV and/or hepatitis transmission. No hepatitis B or C or HIV transmissions have been reported with the use of PCCs and APCCs over the last 16 years in the United States.

Recombinant factor VIIa (NovoSeven), is made by recombinant DNA technology. The drug, which was licensed for use in patients with inhibitors to factor VIII or IX and available in the United States since 1999, has been shown to be effective in the treatment of both minor and life-threatening bleeding. No human plasma proteins are used in its production, and it is not stabilized with albumin. Thus, the risk of transmission of human viruses is essentially zero. Multiple doses can be required to stop bleeding depending on the situation.

It is important to note that the proper diagnosis and treatment of inhibitors is complex, and there are many variables affecting treatment choice; no two patients or situations are identical. In all cases, these choices should be discussed with appropriate healthcare providers with expertise in this area.

Emicizumab (HEMLIBRA®)

In November of 2017, the U.S. Food and Drug Administration approved HEMLIBRA® for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors. While existing factor therapies are delivered intravenously, HEMLIBRA® is unique in that it is administered subcutaneously via an injection just under the skin.

HEMLIBRA® is a laboratory-engineered protein that works by performing a key function in the clotting cascade that is normally carried out by the FVIII protein, which is deficient in individuals with hemophilia A. The “cascade” is an intricate series of chemical and molecular

reactions between clotting factors that lead to the formation of viable clot. In this case, HEMLIBRA® binds to and bridges two other key clotting proteins, activated factor IX and factor X, important components of the cascade normally performed by FVIII.

Please refer to NHF's Medical and Scientific Advisory Council's Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors