

Longer-Acting Factor IX Products on Prophylaxis Regimens

by Dr. David Clark

We are entering a new era in treatment of hemophilia. Prior to the 1960s, the only real therapy for hemophilia B was plasma, which was not very effective and had to be administered in a hospital setting. Starting in the 1960s, plasma-derived factor IX concentrates became available, which allowed patients to treat themselves at home, a significant improvement in quality of life. However, in the early to mid-1980s, it was recognized that plasma-derived products were at risk for contamination by HIV and other viruses.

This led to the development of improved viral screening and inactivation methods, and eventually to recombinant products, making treatment much safer. These safer products also led to the more widespread use of prophylactic treatment, which significantly reduced joint damage and other negative aspects of living with hemophilia.

Now, with the licensure of Biogen Idec's Alprolix we

are entering the era of longer-acting products. Two other longer-acting recombinant products are also in the pipeline, CSL Behring's rFIX-FP and Novo Nordisk's N9 GP. Alprolix obtains its longer half-life by being fused to a recombinant Fc molecule, part of an antibody molecule, while rFIX-FP is similarly fused to recombinant albumin. Both antibodies and albumin have half lives of about three weeks in normal circulation, much longer than the typical 18 to 24 hour half life of factor IX.

N9-GP is glyco-pegylated, which means that it has polyethylene glycol (PEG) molecules attached to the carbohydrate side chains of the factor IX molecule. The PEG side chains make the size of the factor IX molecule too large to be cleared by the kidneys and also interfere with clearance in the liver. All three products are also expected to have higher recoveries meaning that less needs to be infused to produce a given level of factor IX in the bloodstream.

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These new products have the potential to radically modify prophylactic treatment of hemophilia B. The obvious advantage is less frequent infusions, but that can have impacts in various less-obvious ways. A recent journal article (Carcao M, Changing paradigm of prophylaxis with longer acting factor concentrates. *Haemophilia* 20(Suppl. 4) 99-105.) reviewed some of the expected changes.

The new products will require infusions only every one to three weeks depending on the product and the patient. Because every patient reacts differently, individualized dosing has become more common with prophylactic treatment. This will be even more important with longer-acting products.

Pharmacokinetic studies are performed to determine the actual lifetime of a product in the patient's bloodstream. The level of factor needed to prevent bleeding may also be determined. While most patient's bleeding is controlled with trough levels of $>1\%$, some patients need higher levels and some patients need less. We can now also consider higher trough levels for everyone. Because the level of factor IX falls off more slowly, patients will have low factor levels for longer periods of time, which could expose them to a higher risk of bleeding unless the trough level is increased.

The longer dosing intervals should also make it easier to adhere to the dosing schedule, leading to better overall outcomes and less chronic pain. It may no longer be important to infuse in the

morning, which can be burdensome for families getting ready for work and school. Travel should become easier with less need to carry along large amounts of factor. Longer-acting products may also make it easier for patients currently treated on demand to switch to prophylaxis.

The need for less frequent venous access might also make it easier to start children on prophylaxis at an earlier age. It is known that the earlier prophylaxis begins, the better the long term outcomes. The need for frequent dosing with today's products leads to the need for central venous access devices or ports for many children. Although ports are a significant help in performing infusions, they can be problematic, being associated with mechanical failures, infections and thrombosis. With less frequent dosing, more children may be able to go without a port. Fewer clinic visits will also be required for those patients starting out who can't receive infusions at home.

Once additional longer-acting products are on the market, one of the questions physicians and patients will have to consider is how to choose the appropriate product. That may depend on cost and availability, as well as on how a specific product works for the patient. It is not yet known whether the new products can be considered interchangeable. There is also currently little known about the effect of the various products on inhibitor development, but that could also become a factor.

It will be interesting to see what happens with the cost of the longer-acting products. Biogen Idec has announced that the cost of Alprolix will be approximately the same on a yearly basis as the cost of prophylaxis with the current short-acting products. Whether that will continue to be the case once other longer-acting products are available remains to be seen. These products could also have an influence on the cost of the current short-acting products, which may see reduced prices to remain competitive. That could allow developing countries to treat more patients.

Longer-acting factor IX products have the potential to revolutionize the treatment of hemophilia B. All of the potential changes may not be known until the products become more widely used. It will be an interesting time that will hopefully see further improvement in the quality of life for patients with hemophilia. 🐾

Hemophilia and the Dentist

By Chris Roland

As the Director of Dental Services at St Jude, my initial exposure to hemophilia came about in dental school and my pediatric dental residency, but my familiarity with the condition has been solidified after working at St Jude for 12 years.

For most people, life has given them so many gifts that they take for granted. Sight, hearing, and general health are a few easy ones to mention. We take for granted these things until we realize we have lost them or we never had them to begin with. Hemophilia is a condition that once you have it, life seems to be even more of a gift to steward and treasure. It is filled with daily and routine inconveniences. One of these is dentistry. For most, a dental visit consists of going to get a check-up and an occasional filling. No big deal, unless you have conditions that complicate the matter. Depending on the procedure, accommodations need to be considered when taking care of a hemophilia patient. I would like to offer suggestions when you are choosing a dentist and what you need to consider when you have hemophilia.

When a dentist looks at a chart and reads "Hemophilia," the provider has to consider and address several issues. Don't assume the dentist understands your condition as well as you do. Give them thorough information, even if you don't think they will need it. You need to be ready to address the following questions:

1. What is your diagnosis and how long have you had the condition?
2. What medications do you take and how often?
3. How often do you brush and floss?
4. What does your diet consist of?
5. Do you have any lesions in the mouth that have not healed well?
6. What dental procedures have you had previously?
7. Were there any medicines or replacement drugs used to complete the dental procedure?
8. Were there any complications during or after a dental procedure?



9. What are the issues and complications you have experienced with your diagnosis?
10. What are your concerns before having dental treatment completed?

For hemophilia patients, dentists will have primary concerns of decreasing infection and bleeding. Due to an increased chance for infection, antibiotics may be indicated to facilitate healing. For local control of bleeding the dentist uses local anesthetics, oxidized cellulose materials like surgical, and sutures when the gums are involved or extractions are completed. For the systemic management of the patient's diagnosis, the dentist will work with your physician to develop a plan to control potential issues before, during and after dental treatment. The best approach to your dental health is prevention. To conclude, here are a few prevention suggestions I would like to offer:

1. Make sure you brush and floss regularly (two times a day)
2. Eat a healthy and balanced diet
3. Limit your sugar intake, including sodas and juices
4. Drink a lot of water
5. See your dentist on a regular basis for visits 🦷