The New Sub-Q Treatments For Hemophilia

By Chad Blair

As any person or family member of an individual with hemophilia and a Facebook account is well aware there have been a few deaths involving people on the new subcutaneous hemophilia treatments. Many people in the hemophilia community and of course several of the manufacturers for traditional clotting factor products have been sounding alarms and pointing fingers. We are stepping back, examining the facts and seeing just where the truth lays.

To start off there are currently two different subcutaneous products that have been in the news recently, Genentech's (a subsidiary of Roche) Emicizumab and Alnylam's Fitusiran, While these two products are both administered subcutaneously, they are completely different lines of technology, they work in different ways, and must be evaluated individually.

Background

Since hemophilia was first discovered the largest advancements in hemophilia treatments have been the advancement in the production of clotting factor concentrates. The First concentrates were derived from human plasma and even today the proteins used to treat hemophilia have not changed dramatically nor has their route of administration been altered. Even the newest generation recombinant antihemophilic clotting factor products are remarkable facsimiles[1] using a protein molecule with a structure similar to plasma derived proteins, and must be injected directly into a vein.

A person's immune system may become sensitive to these antihemophilic factor proteins and remove them from the body as though they did not belong there. In these cases, called inhibitor cases (which show up in approximately 20% of the patients exposed to clotting factor)[2], bleeding events become harder to control because the immune system neutralizes the standard treatments, which are referred to as replacement treatments. When this is the situation the most effective way to treat bleeding to date has been the use of what are called bypassing agents. A clotting factor protein product that bypasses the need for the missing product. Bypassing agents stimulate thrombin production despite the lack of one of the clotting factor proteins.[3] This increase in thrombin production can increases clot formation and has been linked to thrombotic events in people with no clotting factor deficiency.[4]

There are many mechanisms the body uses to control the clotting cascade and prevent over clotting. These agents work to suppress the active clotting when it is not needed and maintain a balance in hemostasis (prevention of bleeding) and thrombosis (over-clotting). These mechanisms are complicated as a whole as different signals ramp up and slow down production of different "blood thinning" agents.

The following are the results of my own research and discussions the Committee of Ten Thousand had with directly the companies involved.

Comparing Functionality

Emicizumab (formerly ACE 910 while still in trials) uses a molecule that could be described as mimicking the function of the Factor VIII protein while disguising itself as an antigen so the body doesn't react to it. In effect, Emicuzumab steps directly into the hole made by the missing clotting factor VIII for Hemophilia A patients. Emicuzumab is only for Hemophilia A patients and is not intended for use in Hemophilia B patients or any other factor deficiencies.

Fitusiran inhibits the body's ability to prevent clotting by blocking antithrombin. This increases the rate of clot formation and under Alnylam's theory "balances" the clotting for individuals with bleeding disorders. At the annual Hemophilia Federation of America educational symposium Alnylam actually portrayed just that with a graphic of a teeter-totter with all of the clotting factors on one side and all of the mechanisms for preventing clotting on the other. Under this line of thinking, blocking antithrombin essentially balances the teeter-totter when there is a clotting factor protein missing from the other side.

The Real-life Complications

While both of these products have had severe adverse events during the trials resulting in thrombotic events and did cost people their lives, we have to look at how and why this occurred. The thrombotic events with Emicuzumab occurred when people with inhibitors were on the Emicuzumab treatment were given another product containing activated Factor IX due to break through bleeding. When we understand that Factor VIII's roll in the clotting cascade is binding activated Factor IX to Factor X and that is what Emicuzumab is suppose to do, we can see that an influx of activated Factor IX would cause thrombotic events. Normally regardless of how much Factor VIII is in a person's body, it cannot bind Factor IX molecules to Factor X molecules unless the Factor IX is activated first and even then, the supply of activated Factor IX is limited. The thrombotic events in this case were similar to what you would expect if you gave large amounts of activated Factor IX to someone who did not have hemophilia at all.

Fitusiran also had a severe thrombotic event during clinical trials. A patient had what is believed to be a breakthrough bleed and infused a factor to stop the bleeding. If we use Alnylam's own teeter-totter simile we can see that if the teeter-totter was balanced prior to the bleed, the use of factor would completely unbalance the equation. To our understanding, after infusing his typical factor product the person was experiencing head and vision issues and went to the hospital. When the person arrived he was misdiagnosed, the thrombotic event was thought to be a bleeding problem instead of a clotting problem. The hospital gave the patient more factor and made the problem even worse. Even though Alnylam's simile is a very simplistic (possibly too simplistic) view of how clotting function works in the body, it still illustrates a fatal flaw. In the event of injury or breakthrough bleeding, factor cannot simply be administered as it has for years to fix the problem without swinging the teeter-totter far over to the thrombotic side.

Company Responses and Possible Fixes.

Emicuzumab has gotten a lot of flak on social media due in large part to competitors' posts. While there were thrombotic events during the clinical trials, the almost certain cause has been determined and they now know not to use bypassing agents that contain activated Factor IX in the event of breakthrough bleeding. This has been the directive from Genentech/Roche and seems appropriate and a very easy fix.

The issue with Fitusiran is a more recent development. Alnylam has halted the clinical trial until they fully understand how the thrombotic event was caused and how to prevent this again in the future. Some possibilities lay with injecting antithrombin to neutralize the effects of Fitusiran and then treat the hemophilia patient normally with the factor they are deficient in. It may seem somewhat counterproductive to administer a medication that inhibits clotting in order to treat a hemophilia patient's bleed but it is much more acceptable than the thrombotic alternative.

Conclusions

While further trials may need to be completed for Genentech's Emicuzumab to be used on previously untreated patients and on inhibitors patients who have tolerized, it looks like it could revolutionize the life of most Hemophilia A patients. The fear of losing market shares appears to be one of the largest motives behind the negative publicity pushed by competitors.

Fitusiran has had a major set back and a lot of thought will have to be put into how and if to proceed. Alnylam has been up front as a company and quickly halted the trials until they can determine the exact causes and come up with the best plan for moving forward.

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1. Pipe, S W. "Recombinant Clotting Factors." *Thrombosis and Haemostasis.*, U.S. National Library of Medicine, May 2008, www.ncbi.nlm.nih.gov/pubmed/18449413.
2. "Hemophilia." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 7 Dec. 2016, www.cdc.gov/ncbddd/hemophilia/inhibitors.html.
3. Hoffman, M, and Y Dargaud. "Mechanisms and Monitoring of Bypassing Agent Therapy."*Journal of Thrombosis and Haemostasis : JTH.*, U.S. National Library of Medicine, Aug. 2012, www.ncbi.nlm.nih.gov/pubmed/22632160.
4. Dutta, T. K., and S. P. Verma. "Rational Use of Recombinant Factor VIIa in Clinical Practice."*Indian Journal of Hematology & Blood Transfusion*, Springer India, June 2014, www.ncbi.nlm.nih.gov/pmc/articles/PMC4022918/.