boston hemophilia center

ISSUE #11 • SPRING 2016

CENTERPOINTS

And Now for Something Completely Different

Ellis Neufeld, MD, PhD, Medical Director of the Boston Hemophilia Center

By Ellis Neufeld, MD, PhD

As regular BHC Newsletter readers know, several new factor products have come to market in the last three years, and several more are expected before 2018. Among the new factor products are several which will circulate for longer in the blood after infusion, making less frequent infusions possible.

But beyond new factors are exciting new approaches, now in early stages of clinical trials, which could possibly make factor infusions a thing of the past for some patients.

Bifunctional Antibody (ACE-910, Genentech/ Roche), as a replacement for factor VIII. The main job of factor VIII in our blood is to speed the blood clotting reaction by bringing together two other proteins in the coagulation pathway, namely activated factor IX and factor X. This role of factor VIII allows blood clotting to progress much faster than can otherwise occur - a few thousand times faster, which is to say that blood which should clot in seconds or minutes can take days to clot without factor VIII. Clever molecular biology techniques are used in this case to make a modified version of an IgG or antibody molecule, similar to the antibodies we already have in our bodies to fight off germs or respond to vaccines. Antibodies are Y-shaped proteins. Ordinarily the two arms of the Y recognize the same targets. But molecular engineering allows one end of the antibody to recognize factor IXa, and the other arm factor X, bringing the two together. The resulting drug, called ACE-910, is said to have two jobs ("Bifunctional") and while it is somewhat less efficient than regular factor VIII, the difference in efficiency is easily made up by giving more. Antibodies are very stable molecules compared to factor VIII, and can be given subcutaneously instead of intravenously. Early results from phase 1 clinical trials are extremely encouraging, with good safety profiles and much less bleeding so far, in the treated patients. In addition, as a huge added potential bonus of this new approach, patients with hemophilia A and inhibitors are likely to respond just as well as patients without inhibitors, because inhibitors only recognize factor VIII, not this new molecule.

New molecules that tip the balance toward clotting from bleeding. In persons without hemophilia, there is a tightly regulated balance of factors like VIII and IX that promote blood clots, and a group of proteins that inactivate clotting factors to prevent clots from forming where they do not belong (in the veins and arteries of our bodies, for example). Studies in experimental animals have shown that the balance can be tipped by lowering the levels of these anticoagulant proteins, and this in turn can lead to less bleeding in hemophilia. At least two of these approaches have now come to human clinical trials, and show real promise for reducing bleeding. A company called Alnylam is using an approach of

>>> continued on page 2

Table 1 New Factor Products

Longer-acting Factor VIII
Eloctate (Biogen-Idec, 2014)
Adynovate (Baxalta, 2016)

Longer-acting Factor IX
Alprolix (Biogen-Idec, 2014)
FIX-albumin Fusion Protein (CSL, expected 2016)

New brands/preparations of standard-half-life factor VIII
NovoEight (Novo Nordisk)
Nuwiq (Octapharma, 2015)
Kovaltry (Bayer, expected 2016)

New brands/preparations of standard-half-life factor IX
Rixubis (Baxalta, 2013)
IXinity (Emergent, 2014)

Recombinant vonWillebrand factor
Vonvendi (Baxalta, approved 2015, expected availability 2016-17)

boston hemophilia center

Clinical Research Corner

By Revital Freedman, PhD

The Boston Hemophilia Center conducts a number of clinical trials pertaining to bleeding disorders. Bleeding disorders are caused by genetic mutations that result in coagulation factor deficiencies. In other words, because of a change in the DNA, a patient does not produce the factors needed for preventing blood loss in case of a cut, injury, or spontaneous bleed. The clotting factors are proteins that circulate in the blood, and once activated, are responsible for blood clotting. There are 13 clotting factors (numbered I-XIII), but a shortage or complete deficiency in one of them is enough to cause a bleeding disorder. The most common bleeding disorders are Hemophilia A and Hemophilia B which are caused by factor VIII and factor IX deficiencies, respectively. von Willebrand factor is another protein that results in a disorder called von Willebrand disease if it is completely absent or present at insufficient levels in the blood.

The clinical trials that take place at BHC are open for the adult and pediatric populations, and they range from observational studies to advanced studies like gene therapy. These studies are aimed at collecting information about the factor deficiencies and finding therapies for bleeding disorders such as those discussed above.

Two of our largest studies are the Registry for Bleeding Disorders Surveillance and My Life Our Future. The Registry for Bleeding Disorders Surveillance is funded by the Centers for Disease Control (CDC). The purpose of this study is to monitor the health status of patients with bleeding disorders so we can better understand their health issues. Participants in this study are requested to donate a blood sample and fill out a questionnaire. In the questionnaire, we ask the participant to share his medical history, so later on, we can cross check and compare the information given by many different individuals to predict the prognosis and risk factors specific to the disease.

Another clinical study conducted at BHC is My Life Our Future. This study is partnered with the American Thrombosis and Homeostasis Network (ATHN) and is sponsored by Biogen Idec. The purpose of this study is to collect donated blood samples from participants with hemophilia A or B and build a repository of blood samples that will be used to conduct genome research about hemophilia. The Boston Hemophilia Center will receive each patient's hemophilia genotype and will share the results with each participant individually.

In the next BHC Newsletter, we will describe more clinical trials in which you may want to participate and contribute to the growing research base of hematological disorders.

Revital Freedman, PhD, joined BHC as a Research Specialist. Revital earned her doctorate degree in Chemistry from Bar Ilan University in Israel, and continued with postdoctoral studies, where she conducted research in medicinal chemistry and drug development at the Hematology Translational Research Laboratory at Harvard Medical School. Afterwards, she stayed on as a staff chemist at the BWH Medicinal Chemistry Core where she amassed extensive experience in translational research. In her current position as a research specialist, she provides research support to the clinical research staff.

Something Completely Different

<<< continued from page 1

subcutaneous infusions of short pieces of modified nucleic acid every few weeks. These components travel to the liver and shut off the anticoagulant called antithrombin. Other companies are using antibodies to inhibit an anticoagulant called "Tissue Factor Pathway Inhibitor".

Gene Therapy approaches are also moving forward, and represent yet another set of new possibilities for hemophilia treatment. We will cover these approaches in a separate newsletter article.

It is too early to predict, and impossible to guess, how these clinical trials will come out. But the answers about both the safety and effectiveness of these treatments will be known very soon, and they could dramatically change our treatment strategies for hemophilia A and B. Stay tuned!

A great way to learn more about clinical trials that might be of interest to you is to check them out at Clinicaltrials.gov. Your BHC clinicians are also happy to answer questions about clinical research.

Table 2. New Non-Factor Hemophilia Treatment Strategies in clinical trials or early development, 2016

Bifunctional Antibody (ACE-910) for factor VIII deficiency with inhibitors* (Genentech/Roche); if successful, subsequent trials will evaluate patients without inhibitors

Antisense oligonucleotide to antithrombin (Alnylam)

Inhibitors of Tissue-factor Pathway Inhibitor (TFPI) (several companies)

Gene Therapy strategies for factor IX* and Factor VIII

***Clinical trials available at Boston Hemophilia Center**

New Staff at BHC

Amanda Stahl, MSW, LICSW, joined the Boston Hemophilia Center (BHC) team in November, 2015, as the adult hemophilia social worker, replacing Christine Mitchell. A "double eagle", Amanda earned both her BA and MSW from Boston College. After graduating with her MSW in 2010, Amanda moved to California and worked at the Santa Clara Valley Medical Center Homeless Clinic and at Stanford Hospital in inpatient general medicine. After returning to Boston in 2013, Amanda worked on the general medicine service at BWH for 3 years. When not at work, Amanda and her husband are busy taking care of their 6 month old baby, Claire. She can be reached at # 617-732-7197.

Erica Hallsen is newly-employed at BHC as our Hemophilia Administrative Assistant. Prior to this, Erica was a surgical technologist in area hospitals. She is familiar with the healthcare system and will be a valuable asset to our Center. Erica is already busy scheduling patient appointments, providing administrative support, and handling phone calls. You can reach Erica at # 617-278-0707.

Peg Geary, MA, MBA, MPH, is currently a Project Manager at our Center. Peg has had thirty years of experience in healthcare, twenty of which have been in the hemophilia field. She has performed various roles including clinical social work, grant writing, administration and, most recently, served as the CDC Regional Coordinator for New England. Peg has a special interest in education, research, and working with persons in the hemophilia community. She has given many presentations on the local and national levels and has published several articles. Outside of work, Peg enjoys spending time with her husband, two adult sons and her network of friends. She is available at # 617-732-8537.

Emily Coe, Research Coordinator, joined the BHC team in July, 2015, and leads the American Thrombosis and Hemostasis Network (ATHN) projects as well as a number of other hemophilia research studies. She graduated with a B.S. in Health Management and Policy - Public Health from the University of New Hampshire and is currently enrolled part-time in a M.S. program studying Regulatory Affairs for Drugs, Medical Devices and Biologics at Northeastern University. Outside of work, Emily likes to spend time at Lake Winnipesaukee, cross country skiing in the winter and hiking and kayaking in the warmer months.

Nivisha Naik is a Research Associate at Brigham and Women's Hospital and has taken on responsibilities as a Research Coordinator with the BHC team. Nivisha originally moved to Boston to pursue her Master's Degree in Regulatory Affairs at Northeastern University, graduating in 2011. Outside of work, she enjoys cooking, traveling, and kayaking.

"Growing up with Hemophilia & An Inhibitor and Now Serving the Community; A Doctor's Story

An Educational Symposium for BHC patients and families with "Bobby" Duc Q. Tran, Jr., MD, MSc, hosted by the Boston Hemophilia Center on Wednesday, April 20, 2016, from 6:00 - 8:30 p.m. at The Inn at Longwood Medical, Fenway Room, 342 Longwood Avenue, Boston, MA. Dinner will be served and parking provided.

RSVP by Apr. 8th to Peg Geary, Project Manager, # 617-732-8537 or email: mkgeary@partners.org

boston hemophilia center
DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER
BWH BRIGHAM AND WOMEN'S HOSPITAL

Boston Hemophilia Center, Boston Children's Hospital, 300 Longwood Avenue, Fegan 7, Boston, Massachusetts 02115
www.danafarberbostonchildrens.org/hemophilia | www.brighamandwomens.org/hemophilia
www.facebook.com/bostonhemophilia

A Trip to Remember

By Sugastha Govindaraj

Last year, we were the lucky winners of the raffle for a trip to the 67th annual National Hemophilia Foundation conference in Dallas, Texas, in August, 2015. We had never attended any conferences related to bleeding disorders until that point. We had an excellent time, learned a lot of things about the condition, and also met a lot of wonderful people.

We would like to share our experience from the trip and what we learned from the national conference. Let me first say a little bit about ourselves; we have two kids, a son and a daughter, Vasudha, who is a 3 year old girl with Type-3 von Willebrand Disease (vWD). Since our daughter was diagnosed with vWD, we always felt that we were alone in this fight because we did not know many children with her condition. The Boston Hemophilia Center (BHC) was very caring and helped us get through numerous bleeding episodes. An opportunity to attend the NHF conference was a huge eye opener for us. We met a few patients and parents of small children with similar conditions. We shared our experiences and exchanged ideas. We felt for the first time that we were not alone and that we could get through this journey. We also met a young lady who has a similar condition and who had given birth to a healthy boy. Meeting her dramatically impacted our lives and gave us great hope that we could fight through this and that our daughter could lead a very healthy and normal life.

This year, the NHF conference had a lot of sessions about vWD and bleeding disorders for women. They had sessions from basic vWD information to gene therapy and advancements in treatments. Thankfully, NHF provided day care at the same locations and their staff were wonderful and very knowledgeable about the kids' conditions. We felt very comfortable leaving our daughter with them so we could focus on attending different sessions. We wanted to get the most out of the conference and so my wife and I split and attended different sessions and gathered as much information as we could. We had an opportunity to meet several renowned doctors in the field, (including our own Dr.Neufeld) and clarified a lot of questions that had come up during our sessions. We also attended group meetings and rap sessions with other patients and learned various tips and techniques to handle nosebleeds and common bleeding problems. With those tips, we were able to successfully navigate through this winter and it gave us so much confidence to handle difficult situations.

The most interesting part of our whole trip was that we met so many New Englanders at the conference and we exchanged our contact information which enabled us to participate in many more community events locally. We also enjoyed the exhibit halls, got an opportunity to talk to many people from the industry, and learned about the recent developments in the medical field.

Once again, we thank BHC for giving us a great opportunity to participate in NHF's annual conference.

Madhu Rajagopalan, daughter Vasudha Madhusudhan, son Saketh Madhusudhan and Sugastha Govindaraj