Factor Nine News

The Coalition for Hemophilia B

SPRING 2020

TOPICS IN HEMOPHILIA B

GEN IX LEADERSHIP PROGRAM

BY ROCKY WILLIAMS

There are some opportunities in life that you simply don't pass up. One of them was this past January, when I joined other members of the Coalition for Hemophilia B community from all over the country to attend the Gen IX Leadership Program in Pigeon Key, Florida.






The Gen IX Leadership Program is one of three annual events that make up the Generation IX Project, which offers individuals with hemophilia B the opportunity to learn from and connect with one another. Sponsored by Medexus Pharma (formerly Aptevo Therapeutics) and facilitated by GutMonkey, the Gen IX Programs have had more than 200 participants since their launch in 2014. What started as one big event has now evolved into three separate annual events—one each on Leadership, Teen/Mentorship, and Advocacy.

Leadership is a big idea, and it can encompass many actions, characteristics, and intentions. This year's program focused on "heroic" leadership – which affirms that anyone and everyone is a leader and that we continually influence and shape those around us. Heroic leaders are self-aware; they question and disrupt the status quo to strive for better, and they embrace and adapt to a changing world. Sometimes they lead by following and supporting others. And, hey – sometimes heroic leaders really do wear capes!

With everything going on in the world right now, there was no better time to assemble leaders with hemophilia B, age 18 to 35, to connect and talk about how we can make a difference in our own lives and in the lives of those around us. The learning sessions and activities taught us about giving constructive feedback, how to recognize someone's preferred communication style, and ways to









push ourselves outside of our comfort zones.

The program focused on teaching the ins and outs of the four pillars of heroic leaders: self-awareness, ingenuity, love, and heroism. We were placed in team-building and problem-solving exercises that tested our mettle and put our newly sharpened skills to the test. The program was educational, very much hands on, and it challenged us to do – and be – better.

The program was inspiring, and it was also FUN! We gathered on a beautiful island teeming with Florida wildlife. We snorkeled, fished, and visited a turtle hospital. One person caught a shark! We made our own capes, we tackled island-wide hero-themed activities, and we grew stronger as individuals, as members of a team, and as leaders of the hemophilia B community.

Our hope is that everyone who participated in the program, and those who participate in the future leave feeling empowered, inspired, and ready to take a leadership role to support the Coalition for Hemophilia B and our community.

"What I like most about the program is the gathering of people with hemophilia from across the country, breaking us out of our comfort zones to be able to work together to complete any task," said Joe, a participant in the program. "With a good team on your side, anything is possible."

Thank you to our generous supporter of this invaluable program!

MEDEXUS PHARMA





Eternal Spirit Award Gala

BY GLENN MONES

On March 5, members and supporters of the Coalition for Hemophilia B gathered in festive celebration for the *2020 Eternal Spirit Award Gala*. The event was held at New York City's spectacular Terrace on the Park. Perched high above Flushing Meadows Park, the site of two World's Fairs, attendees enjoyed vistas of the park with the famed Unisphere globe, Citi Field, the National Tennis Center and the glittering city skyline.

The event theme was *An Evening in Italy*, highlighting the food and music of the "bel paese." Guests enjoyed a delicious and extensive menu of both traditional and contemporary Italian fare. The wonderful entertainment featured a variety of opera and folk singers performing Italian selections.

The formal program included a special welcome by our Chairman, Dr. David Clark. This was followed by the presentation of the Eternal Spirit Award by our President, Wayne Cook. The award is given annually to two deserving individuals who have made significant contributions to the health and well-being of our members. This year's recipients were Mr. Joseph Pugliese and Dr. Robert Sidonio, Jr.

Joe Pugliese is a true friend to our organization and the people we serve. He has provided dedicated service to the hemophilia B community and to the hemophilia community at large for more than forty years. As the President and CEO of the Hemophilia Alliance since 2008, Joe has strengthened the national network of hemophilia treatment centers (HTCs), ensuring that people living with bleeding disorders would have access to quality care for years to come. He also

created the Hemophilia Alliance Foundation which carries out the HTC network's commitment to reinvest in the community at the national and local level.

Dr. Robert F. Sidonio, Jr. has served as the Associate Director of Hemostasis and Thrombosis at Emory University since 2014. Dr. Sidonio's clinical and research interest is in investigating the bleeding phenotype and genotype of women with hemophilia carriage and low VWF. He is also the co-creator of the Atlanta Protocol, which combines Emicizumab and FVIII for immune tolerance and has served as the lead or co-PI for a wide variety of other studies and clinical trials. A frequent presenter at Coalition programs, he has shed new light and understanding on the diverse factors that contribute to bleeding.

The evening also featured the presentation of the Dr. William N. Drohan Scholarship. The scholarship's namesake was a well-known microbiologist and educator who lost his battle with metastatic lung cancer at the age of 60. He was a pioneer in using molecular biology to produce recombinant proteins and a visionary scientist who dedicated his life to improving the safety of blood and blood products. Dr. Drohan also served as a member of the board of The Coalition for Hemophilia B and was instrumental in the Coalition's creation.

Each year, we award four or more scholarships to students with hemophilia B and/or their siblings. Over the past 13 years, we have distributed $285,000 in scholarships. The scholarships are funded in part through the proceeds of the gala, including the generous support of our wonderful sponsors. 2020 sponsors included Aptevo, Pfizer and

















Sanofi Genzyme (Diamond), CSL Behring, CVS Health and Novo Nordisk (Gold), uniQure (Bronze), Accredo (Benefactor), and Grifols and Rarity Health (Friends).

Proceeds from the evening also support the *BCares* Emergency Assistance Fund and the *BVoice* Advocacy Program. *BCares* provides urgent help to individuals or families affected by hemophilia B facing a variety of crisis situations. This fund has been especially crucial as needs have skyrocketed during the current COVID-19 pandemic. *BVoice* organizes community members and provides information and tools to allow them to advocate with elected officials and others. This program has recently focused on ensuring uninterrupted access to healthcare during the crisis.

Our recollections of this special evening remind us of the warmth and joy we feel when we come together as a community. Recent events have necessitated the introduction of new and creative ways of keeping us all connected even when we can't be physically together. These technologies allow us to share information in ways we never dreamed possible. We encourage all community members to join us virtually at the many programs we are offering. Of course, we also look forward to the time, hopefully very soon, when we may again share friendship and support in the same physical spaces across our beautiful country.

RIXUBIS® [Coagulation Factor IX (Recombinant)] Important Information

What is RIXUBIS?

RIXUBIS is an injectable medicine used to replace clotting factor IX that is missing in adults and children with hemophilia B (also called congenital factor IX deficiency or Christmas disease).

RIXUBIS is used to control and prevent bleeding in people with hemophilia B. Your healthcare provider may give you RIXUBIS when you have surgery. RIXUBIS can reduce the number of bleeding episodes when used regularly (prophylaxis).

Detailed Important Risk Information for RIXUBIS® [Coagulation Factor IX (Recombinant)]

Who should not use RIXUBIS?

You should not use RIXUBIS if you

- are allergic to hamsters
- are allergic to any ingredients in RIXUBIS.

Tell your healthcare provider if you are pregnant or breastfeeding because RIXUBIS may not be right for you

What should I tell my healthcare provider before using RIXUBIS?

You should tell your healthcare provider if you

- have or have had any medical problems
- take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies
- have any allergies, including allergies to hamsters

What should I tell my healthcare provider before using RIXUBIS? (cont'd)

- are breastfeeding. It is not known if RIXUBIS passes into your milk and if it can harm your baby
- are pregnant or planning to become pregnant. It is not known if RIXUBIS may harm your unborn baby
- have been told that you have inhibitors to factor IX (because RIXUBIS may not work for you).

What are the possible side effects of RIXUBIS?

Allergic reactions may occur with RIXUBIS. Call your healthcare provider or get emergency treatment right away if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, lightheadedness, dizziness, nausea, or fainting.
Some common side effects of RIXUBIS were unusual taste in the mouth and limb pain.

Tell your healthcare provider about any side effects that bother you or do not go away.

Your body may form inhibitors to factor IX. An inhibitor is part of the body's defense system. If you form inhibitors, it may stop RIXUBIS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for development of inhibitors to factor IX.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see RIXUBIS Important Facts on the following page and discuss with your healthcare provider.

Takeda

RIXUBIS
[COAGULATION FACTOR IX (RECOMBINANT)]
MOVING FORWARD

Important facts about RIXUBIS®:

RIXUBIS
[COAGULATION FACTOR IX (RECOMBINANT)]

This leaflet summarizes important information about RIXUBIS. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider.

What is RIXUBIS used for?

RIXUBIS is a medicine used to replace clotting factor (Factor IX) that is missing in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease. Hemophilia B is an inherited bleeding disorder that prevents blood from clotting normally. RIXUBIS is used to prevent and control bleeding in people with hemophilia B. Your healthcare provider may give you RIXUBIS when you have surgery. RIXUBIS can reduce the number of bleeding episodes when used regularly (prophylaxis).

Who should not use RIXUBIS?

You should not use RIXUBIS if you
- are allergic to hamsters
- are allergic to any ingredients in RIXUBIS

Tell your healthcare provider if you are pregnant or breastfeeding because RIXUBIS may not be right for you.

What should I tell my healthcare provider before using RIXUBIS?

You should tell your healthcare provider if you
- have or have had any medical problems
- take any medicines, including prescription and non-prescription medicines, such as over-the-counter medicines, supplements or herbal remedies
- have any allergies, including allergies to hamsters
- are breastfeeding. It is not known if RIXUBIS passes into your milk and if it can harm your baby
- are pregnant or planning to become pregnant. It is not known if RIXUBIS may harm your unborn baby
- have been told that you have inhibitors to factor IX (because RIXUBIS may not work for you).

What is the most important information I should know about RIXUBIS?

Allergic reactions have been reported with RIXUBIS. Stop using the product and call your healthcare provider or get emergency treatment right away if you get a rash or hives; rapid swelling of the skin or mucous membranes; itching; tightness of the throat; chest pain or tightness; wheezing; difficulty breathing; low blood pressure; lightheadedness; dizziness; nausea; vomiting; tingling, prickling, burning, or numbness of the skin; restlessness; or fainting.

Your body may form inhibitors to factor IX. An inhibitor is part of the body's defense system. If you form inhibitors, it may stop RIXUBIS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor IX.

The use of factor IX containing products has been associated with the development of blood clots. Talk to your doctor about your risk for potential complications and whether RIXUBIS is right for you.

What are the possible side effects of RIXUBIS?

Some common side effects of RIXUBIS were unusual taste in the mouth, limb pain, and atypical blood test results. Tell your healthcare provider about any side effects that bother you or do not go away. These are not all the side effects possible with RIXUBIS. You can ask your healthcare provider for information that is written for healthcare professionals.

What else should I know about RIXUBIS?

Consult with your healthcare provider to make sure your factor IX activity blood levels are monitored so they are right for you.

You should be trained on how to do infusions by your healthcare provider or hemophilia treatment center. Many people with hemophilia B learn to infuse their RIXUBIS by themselves or with the help of a family member.

Call your healthcare provider right away if your bleeding does not stop after taking RIXUBIS.

Medicines are sometimes prescribed for purposes other than those listed here. Do not use RIXUBIS for a condition for which it is not prescribed. Do not share RIXUBIS with other people, even if they have the same symptoms that you have.

The risk information provided here is not comprehensive. To learn more, talk about RIXUBIS with your healthcare provider or pharmacist. The FDA-approved product labeling can be found at https://www.shirecontent.com/PI/PDFs/RIXUBIS_USA_ENG.pdf or by calling 1-877-825-3327.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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Takeda

ACKNOWLEDGMENT IS POWER

We always say that knowledge is power. Acknowledgment is power, too. We at the Coalition for Hemophilia B also want everyone to know that we SEE you, we HEAR you and we STAND with you. Hand in Hand, we need to Unite and Shine our Light for Change Together. TOGETHER – OUR VOICE – OUR ACTIONS – NOW.

WE'RE WITH YOU!

BY KAREN BROGNO AND ROCKY WILLIAMS

It means everything to us to be able to offer resources and programs to help you and your family. While we are not ready to resume in-person meetings yet, we are gathering together virtually — often multiple times a week!

Starting in May, we have hosted regular Saturday trivia nights over Zoom. Participants from across the country tuned in to chat, share stories, and compete in trivia games. We learned about everything from movies to food — and, of course, hemophilia and health. There was plenty of laughter as we battled for a chance to win prizes.

With sponsorship from Medexus, we have also hosted several Zoom Travel Adventures, a Generation IX virtual hangout with GutMonkey, and presentations on health insurance basics and the needs of caregivers for persons with chronic illness, presented by BioMatrix.

In the travel adventures, our pilot Christian Harris and the CHB flight crew led us in first-class fun as we explored exciting destinations online. The virtual hangout session had us literally jumping out of our seat to share fun stories about ourselves, and the sessions on insurance and chronic illness were educational and very impactful.

We also want to give a special shout-out to community member Rick Starks, who Zoomed a series of Tai Chi sessions from his home, and Robert Friedman, who shared sessions on stress management and relaxation.

We can't physically be together right now, but it's never been more important to unite and build our community. Thank you to everyone who has participated in these virtual events — and if we haven't seen you yet, we invite you to join us for future online events! Everyone at CHB is here for you!

IDELVION®
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

LONG-LASTING BLEED PROTECTION

FOR THE HERO WITHIN

THE ONLY EXTENDED HALF-LIFE FACTOR IX THERAPY THAT DELIVERS

0 SPONTANEOUS **BLEEDS***

Whether dosed every 7 or 14 days in clinical trials

UP TO **14** **DAY DOSING**† FDA APPROVED

Dosing schedules that fit your lifestyle

20% STEADY-STATE **TROUGH LEVELS** WITH 7-DAY PROPHYLACTIC USE‡

High and sustained steady-state FIX levels

*Zero median annualized spontaneous bleeding rate when dosed at 7 or 14 days in clinical trials.
†Once well controlled (1 month without spontaneous bleeding or requiring dose adjustments on a weekly dose of ≤40 IU/kg), people 12 years and older can be transitioned to 14-day dosing.
‡The average dose for people receiving prophylaxis every 7 days was 37 IU/kg and every 14 days was 73 IU/kg.
§Hemophilia FIX Market Assessment. Third-Party Market Research.

Is it time for a switch? Learn more at IDELVION.com

#1 FACTOR IX CHOICE WHEN CHANGING THERAPY§

Important Safety Information

IDELVION is used to control and prevent bleeding episodes in people with hemophilia B. Your doctor might also give you IDELVION before surgical procedures. Used regularly as prophylaxis, IDELVION can reduce number of bleeding episodes.

IDELVION is administered by intravenous injection into the bloodstream, and can be self-administered or administered by a caregiver. Do not inject IDELVION without training and approval from your healthcare provider or hemophilia treatment center.

Tell your healthcare provider of any medical condition you might have, including allergies and pregnancy, as well as all medications you are taking. Do not use IDELVION if you know you are allergic to any of its ingredients, including hamster proteins. Tell your doctor if you previously had an allergic reaction to any FIX product.

Please see additional Important Safety Information and brief summary of prescribing information on adjacent page and full prescribing information including patient product information at IDELVION.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. **Visit www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Important Safety Information (cont'd)

Stop treatment and immediately contact your healthcare provider if you see signs of an allergic reaction, including a rash or hives, itching, tightness of chest or throat, difficulty breathing, lightheadedness, dizziness, nausea, or a decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. You might need to be tested for inhibitors from time to time. IDELVION might also increase the risk of abnormal blood clots in your body, especially if you have risk factors. Call your healthcare provider if you have chest pain, difficulty breathing, or leg tenderness or swelling.

In clinical trials for IDELVION, headache was the only side effect occurring in more than 1% of patients (1.8%), but is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away, or if bleeding is not controlled with IDELVION.

IDELVION®, Coagulation Factor IX (Recombinant), Albumin Fusion Protein

Initial U.S. Approval: 2016

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IDELVION safely and effectively. Please see full prescribing information for IDELVION, which has a section with information directed specifically to patients.

What is IDELVION?

IDELVION is an injectable medicine used to replace clotting Factor IX that is absent or insufficient in people with hemophilia B. Hemophilia B, also called congenital Factor IX deficiency or Christmas disease, is an inherited bleeding disorder that prevents blood from clotting normally.

IDELVION is used to control and prevent bleeding episodes. Your healthcare provider may give you IDELVION when you have surgery. IDELVION can reduce the number of bleeding episodes when used regularly (prophylaxis).

Who should not use IDELVION?

You should not use IDELVION if you have had life-threatening hypersensitivity reactions to IDELVION, or are allergic to:

- hamster proteins
- any ingredient of IDELVION

Tell your healthcare provider if you have had an allergic reaction to any Factor IX product prior to using IDELVION.

What should I tell my healthcare provider before using IDELVION?

Discuss the following with your healthcare provider:

- Your general health, including any medical condition you have or have had, including pregnancy, and any medical problems you may be having
- Any medicines you are taking, both prescription and non-prescription, and including any vitamins, supplements, or herbal remedies
- Allergies you might have, including allergies to hamster proteins
- Known inhibitors to Factor IX that you've experienced or been told you have (because IDELVION might not work for you)

What must I know about administering IDELVION?

- IDELVION is administered intravenously, directly into the bloodstream.
- IDELVION can be self-administered or administered by a caregiver with training and approval from your healthcare provider or hemophilia treatment center. **(For directions on reconstituting and administering IDELVION, see the Instructions for Use in the FDA-Approved Patient Labeling section of the full prescribing information.)**
- Your healthcare provider will tell you how much IDELVION to use based on your weight, the severity of your hemophilia B, your age, and other factors. Call your healthcare provider right away if your bleeding does not stop after taking IDELVION.
- Blood tests may be needed after you start IDELVION to ensure that your blood level of Factor IX is high enough to properly clot your blood.

What are the possible side effects of IDELVION?

Allergic reactions can occur with IDELVION. Call your healthcare provider right away and stop treatment if you get a rash or hives, itching, tightness of the chest or throat, difficulty breathing, light-headedness, dizziness, nausea, or decrease in blood pressure.

Your body can make antibodies, called inhibitors, against Factor IX, which could stop IDELVION from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

IDELVION might increase the risk of abnormal blood clots forming in your body, especially if you have risk factors for such clots. Call your healthcare provider if you experience chest pain, difficulty breathing, or leg tenderness or swelling while being treated with IDELVION.

A common side effect of IDELVION is headache. This is not the only side effect possible. Tell your healthcare provider about any side effect that bothers you or does not go away.

Based on May 2018 revision

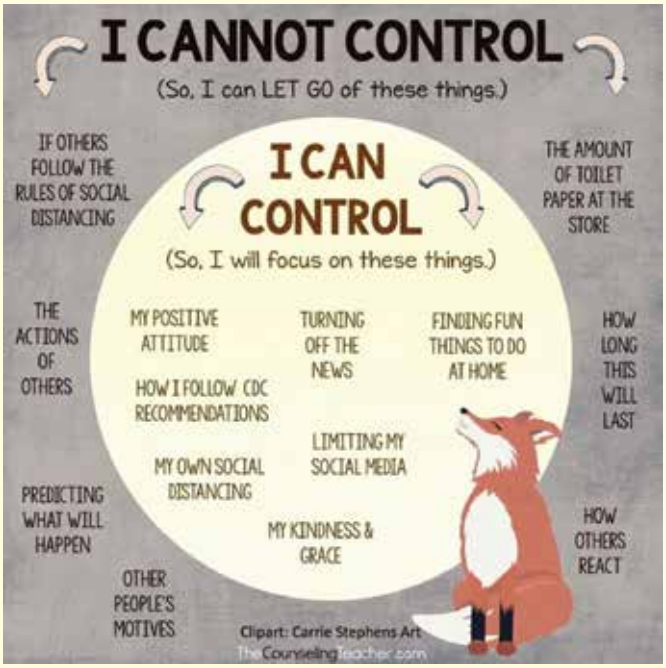
Please see full prescribing information, including FDA-approved patient labeling.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

IDELVION®
Coagulation Factor IX (Recombinant), Albumin Fusion Protein

SURVEY UPDATE

The 2020 survey deadline is extended until October 25, 2020. The survey is now in an easier to complete format. Anyone who completes the updated survey will be automatically entered into a drawing to attend our 2021 Symposium in Orlando, Florida**.** Drawings will be on October 28, 2020. We appreciate your time and your valuable input! Thank you!



COPING WITH UNCERTAINTIES

Anxiety and stress are common among those with a bleeding disorder, and with the twists and turns that mark 2020, the uncertainty about what the future holds may increase those feelings. Yet there is one thing we know: Resources are available to help. We have compiled a list of national telephone help lines and general topics in mental health and COVID-19 stress management in the *Mental Health and Wellness* section of our website hemob.org. We encourage you to refer to them if needed or to reach out by private email to Kim at kimp@hemob.org if you want to talk or need additional resources.

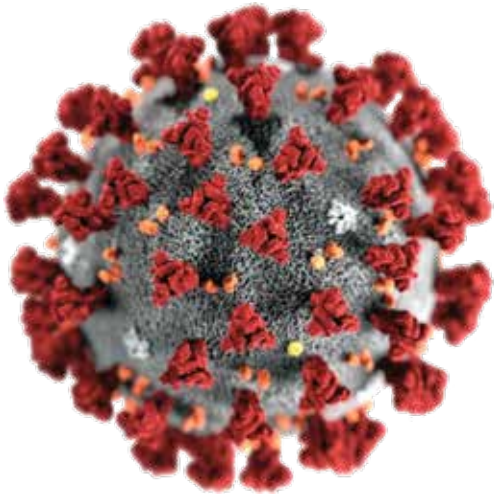
PBS HIGHLIGHTS LIVING WITH HEMOPHILIA

Watch the PBS *Medical Stories* special on hemophilia – *Living a Full Life With a Royal Disease* – on our website now at hemob.org. This episode shares the personal life journey of hemophilia B community member Ben Shuldiner.

HEMOPHILIA AND COVID-19

BY DR. DAVID CLARK

A 35-year-old man in Wuhan, China, who has severe hemophilia A, experienced aching pain in his limbs. Thinking he might be having a bleed, he took his usual dose of factor VIII, but the pain continued. The next day, he felt fatigue, chills, had a low-grade fever; he was vomiting and lost his appetite. For two days he treated himself with oral antibiotics and traditional Chinese medicine. When the fever did not stop, he went to the emergency department, where he was diagnosed with COVID-19. He had no other underlying disease except for hemophilia A, with his left knee as a target joint.



Since there was no room in the hospital, he was treated with intravenous immunoglobulin and sent home to self-quarantine. He was also treated with oseltamivir (an antiviral), cefdinir (an antibiotic), and Lianhua Qingwen (traditional Chinese medicine). On the third day of treatment (7 days after his first symptoms), his appetite suddenly improved and the muscle (limb) pain, vomiting, and chills went away. Two days later, his fever ceased, but he still had a dry cough, difficulty breathing, and chest pain. It took two more weeks for those symptoms to end. In all, it took from January 19th, when his limb pain began, until March 10th, when he was declared asymptomatic. He had no unusual bleeding events during that time. Unfortunately, because of the isolation measures in Wuhan, they lost track of him and thus have no further follow-up to report.[1]

This is the first and, so far, only published report we have of a hemophilia patient with COVID-19. In spite of the patient's underlying hemophilia, the doctors report that his clinical course was typical for COVID patients.

Another article from a group of physicians and specialists treating hemophilia patients in Belgium states: "There is no reason to suspect that the clinical presentation of COVID-19, its severity and complications, are influenced by haemophilia."[2] They go on to present practical, commonsense advice for management of COVID-19 in patients with hemophilia. They recommend that you inform your Hemophilia Treatment Center (HTC) or hematologist of any suspicion or confirmed diagnosis of COVID-19 and involve your doctors in any care decisions.

They also recommend that you practice social distancing as appropriate and possible for your situation. You should continue your regular factor infusions and not delay treating bleeds. You should make sure you have an adequate supply of factor at home in case of shortages or difficulty receiving shipments. You should also maintain physical activities to avoid joint deterioration and prevent muscle loss.

If you need to seek care, it is important to make physicians and nurses aware of your hemophilia and treatment regimen. Also, inform them if you are, or have recently been, involved in any clinical studies. Some medications may interfere with diagnostic tests, especially clotting assays. Your factor product could also interfere with anticoagulants administered to prevent thrombosis (unwanted internal clotting).

We have been learning that in addition to respiratory issues, another significant symptom of COVID-19 is thrombosis. At this point, we're not sure of the cause and whether hemophilia would give you any protection from it. The excess clotting could be caused by other pathways that don't depend on factors VIII or IX. As a compromise between the risks of bleeding and thrombosis, the authors of the Belgium report recommend that hospitalized hemophilia patients' factor levels be kept at 50–100% for factor VIII (hemophilia A) and 30–60% for factor IX, preferably by continuous infusion with short-acting factor

concentrates. Extended half-life (EHL) factor concentrates may be used, but patients' levels should be monitored to determine the appropriate dosing interval. Patients on ventilators should also be monitored for von Willebrand factor (vWF) levels since ventilators can cause a depletion of vWF.

Patients should also be monitored for inhibitor development. The stress of COVID-19 symptoms and treatments, as well as the accompanying inflammation, can spark development of inhibitors, even in patients without hemophilia. It can also cause previously eliminated inhibitors to be re-activated. One patient in Italy, who did not previously have hemophilia but developed acquired hemophilia A after COVID-19 infection, was treated successfully with activated factor VII.[3] Again, a careful balance needs to be maintained between bleeding and clotting.

COVID-19 will also have effects on other aspects of living with hemophilia. Elective surgeries and clinical studies have all been delayed. Some researchers have shifted their focus from hemophilia to COVID-19 for the time being. Meetings and educational programs have been delayed or canceled. It also appears that much of the community could end up in difficult financial situations. I'll end with a quote from an editorial from the World Federation of Hemophilia (WFH): "Our bleeding disorders global community has experienced more than one crisis. This one is as different as it is unexpected. Together we can all face it and learn the necessary lessons from it."[4]

References

The references used for this article are free online. The easiest way to find them is to type the DOI number into your browser. For instance, type in "DOI: 10.1111/hae.14000" without the quotation marks to find the first reference.

1. D. Cui et al., "Clinical Findings in a Patient with Haemophilia A Affected by COVID-19," Haemophilia. DOI: 10.1111/hae.14000.
2. C. Hermans et al., "In-Hospital Management of Persons with Haemophilia and COVID-19: Practical Guidance." Haemophilia. DOI: 10.1111/hae.14045.
3. M. Franchini et al., "The First Case of Acquired Hemophilia Associated with SARS-CoV-2 Infection." American Journal of Hematology. DOI: 10.1002/ajh.25865.
4. C. Hermans et al., "The COVID-19 Pandemic: New Global Challenges for the Haemophilia Community." Haemophilia. DOI: 10.1111/hae.14001

Manufacturers of Plasma-Derived Therapies Unite to Develop a Potential COVID-19 Therapy.

BY GLENN MONES

According to industry press releases, an alliance has been formed by the world's leading manufacturers of plasma-derived therapies to develop a hyperimmune immunoglobulin that can be used to treat the COVID-19 virus. The partnership was initiated by Takeda and CSL Behring, both of whom have several hemophilia therapies in their product portfolios.

Companies who have since joined the group include Biotest, BPL, LFB, and Octapharma. The group will begin to work immediately on developing an unbranded treatment that will have the potential to treat individuals with serious complications from COVID-19, according to the Takeda release.

The companies will devote their own resources to the effort and plan to collaborate with government and academic groups on several activities including clinical trials.

Plasma donations from people who have fully recovered from COVID-19 will be essential to the effort. Their plasma will contain antibodies that can potentially destroy the virus in infected individuals. Individuals interested in donating plasma can visit DonatingPlasma.org to find the nearest licensed plasma collection center to their location.

The Coalition for Hemophilia B applauds this wonderful collaboration. We will continue to provide updates on this important story as they become available.

B VOICE ADVOCACY UPDATE

BY GLENN MONES

From January 29-30, 2020, individuals representing diverse segments of the hemophilia community and those who serve it gathered in Washington DC for a Safety Summit to discuss monitoring, educating, and communicating issues around bleeding disorders product safety. The gathering was organized and convened by the National Hemophilia Foundation (NHF) and the Hemophilia Federation of America. The meeting included representatives of the Centers for Disease Control and Prevention (CDC), pharmaceutical manufacturing companies, home healthcare companies, clinicians, patient advocacy organizations, and individuals affected by bleeding disorders. The Coalition for Hemophilia B was represented by Advocacy Manager, Glenn Mones, who also served on a panel about patient notification. The Executive Summary of the meeting has now been released. It can be viewed at https://www.hemophilia.org/sites/default/files/article/documents/SafetySummit_PrelimSummary_2020-04-29_FINAL.pdf.

Among the many findings were the importance of taking a patient-centric role when it comes to safety issues. Patients were also encouraged to take responsibility for reporting adverse events. The final report on the meeting is due by the end of the year.

On February 28, 2020, members of The Coalition for Hemophilia B joined with hundreds of families and individuals affected by bleeding disorders from around the country for NHF's annual *Washington Days* program. We had the opportunity to meet with and educate our elected representatives about hemophilia and the needs of our community. We expressed our support in particular for the *Hemophilia SNF Access Act*, a new piece of legislation in both the House and Senate. The bipartisan bill is designed to address the problems people with bleeding disorders on Medicare encounter when trying to access skilled nursing facilities (SNFs). The proposed law is known as S.3233 in the Senate, where it was introduced by Senators Bob Menendez (D-NJ), Michael Enzi (R-WY), and Sheldon Whitehouse (D-RI), and HR 5952 in the House, where it was introduced by Representatives Darin LaHood (R-IL), Brian Higgins (D-NY), Debbie Dingell (D-MI), and Gus Bilirakis (R-FL).

Unfortunately, no further action has been taken on the legislation in recent months because of the congressional recess and then the need to focus on the pandemic and its ramifications. However, we are hopeful we will be able to help move the bill forward once Congress is able to return to a more normal agenda. The Coalition for Hemophilia B also joined with other national bleeding disorders organizations in sending letters of support to the bill sponsors in both chambers. You can view the letters by visiting our website at www.hemob.org.

Since March, we have ramped up many of our advocacy efforts to help address some of the ways the COVID-19 pandemic is impacting our community and other Americans living with chronic conditions. Through our *B Voice* advocacy program, we have focused our activities on protecting access to care during the crisis and ensuring the health and well-being of the families and individuals we serve.

APLUS Efforts

We are pleased to announce that we are now an active member of the American Plasma Users Coalition (APLUS). APLUS represents more than 125,000 Americans living with chronic disorders who are dependent on plasma protein therapies and their recombinant analogs for their daily living. The national patient organizations that are APLUS members share a common desire to ensure that the patient voice is heard when relevant public policies, regulations, directives, guidelines, and recommendations affecting access to safe and effective therapy and treatment are considered. Other members include the GBS|CIDP Foundation International, the Jeffrey Modell Foundation, the US Hereditary Angioedema Association,

the Immune Deficiency Foundation, the Alpha–1 Foundation, Patient Services, Inc., the Committee of Ten Thousand, the Hemophilia Federation of America, the Platelet Disorder Support Association, and the National Hemophilia Foundation.

APLUS member organizations have been meeting regularly over the internet to share information and strategies to make sure the various therapies we rely on remain available, safe, and reimbursed by insurance and government programs. One recent effort was the creation of a letter to Alex M. Azar, II, Secretary of the Department of Health and Human Services. The letter addresses the importance of protecting the supply of plasma in the United States along with the medicines that are made from it, including antihemophilic factor (AHF).

Legislative Efforts

Our *B Voice* team has also been working with a variety of groups to address the ways Americans living with chronic conditions are being affected by the COVID-19 crisis. As Congress has debated what would be contained in the various stimulus packages, we have worked to make our legislators aware of the needs of people with chronic conditions, urging them to address these needs in their legislation. Some of the items we have requested include universal access to testing and treatment, expanded access to affordable health insurance, protection for healthcare workers, adequate funding for state and local efforts, and many others.

The Heroes Act, passed by the Democrat-controlled House of Representatives on May 16, 2020, reflects some of the things we have been requesting. For example, the act includes provisions that would protect insurance coverage for many Americans who may have recently lost employer-provided coverage or are otherwise uninsured. This would be accomplished through expanded COBRA insurance and a special enrollment period for Marketplace insurance (Obamacare). The Heroes Act also includes a second stimulus payment for families and individuals, plus a variety of other provisions to help families, individuals, essential workers, small businesses, and nonprofits. However, as of the writing of this article, the legislation sits with the Republican-controlled Senate and there is a lot of pushback on many of its provisions. Intense negotiations are anticipated, and we may see significant modifications before the bill reaches its final form, so stay tuned!

Accumulator Adjuster Update

In a setback for this community and many other people with expensive, chronic conditions, the Department of Health and Human Services (HHS) released its Notice of Benefit and Payment Parameters for 2021 final rule (federalregister.gov/d/2020-10045), which allows health plans to implement copay accumulator programs regardless of whether or not generic alternatives are available for a specific condition. These programs, which have been adopted by insurance companies with increasing frequency over the last several years, allow payers to not count copay assistance as an out-of-pocket payment. This means that patients who receive such assistance (i.e., through a manufacturer-sponsored program) will still be responsible for all their copayments until they meet their deductible or out-of-pocket maximum. For many, this can add up to thousands or even tens of thousands of dollars.

Last year, HHS indicated that these programs would not be applied to patients with conditions for which there are only brand-name therapies but no generic equivalents. Hemophilia falls into this category. Unfortunately, this latest rule reverses that guidance and allows insurers to apply accumulator adjusters in all instances. We will be expressing our strong disagreement with this decision and making the case that this unfairly targets people who often can least afford it. It is important that we be able to document examples where patients with hemophilia B have been subjected to these programs. If you think that your insurance company is applying an accumulator adjustment program to you and your family, please let us know.

We are also looking at what federal protections exist for Americans who may be compelled to return to work before it is truly safe, and how these protections may be strengthened and expanded. A Time magazine article from May 6th (*Scared to Return to Work Amid the COVID-19 Pandemic?*) has more information on this issue.

The Coalition for Hemophilia B is committed to empowering our members with the tools and information needed to protect our access to care. Using social media, our website, email, and a variety of publications, we have strived to keep our members “in the loop” about what things are happening at the national and state levels that may impact their lives and the lives of family members. We urge everyone to stay informed by following us on social meeting and visiting our website at www.hemob.org. Please let us know if there are things affecting your family that we may not be aware of yet.

TAKE CONTROL TO A HIGH LEVEL WITH REBINYN®

IN HEMOPHILIA B

Clayton, 34 years old, is a pilot and enjoys hiking and camping in his spare time. Clayton lives with hemophilia B.

Rebinyn® elevates factor levels above your normal levels[a]

+94% Factor IX (FIX) levels achieved after an infusion[b]

83-hr (3.5 day) average half-life in adults[a]

With a single dose of Rebinyn® 40 IU/kg in adults with ≤2% FIX levels[a]

Achieve higher factor levels for longer

Compared with Alprolix®[c], Rebinyn® provides

4x greater factor coverage

6x higher factor levels at 7 days

Image of hemophilia patient shown is for illustrative purposes only.

[a]In a phase 3 study of adults, single dose pharmacokinetics were tested during the first Rebinyn® 40 IU/kg dose in 6 adults.

[b]Based upon a 2.34% increase in factor levels per IU/kg infused in adults.

[c]Based upon a phase 1 study comparing a single 50 IU/kg dose of Rebinyn® to a single 50 IU/kg dose of extended half-life rFIXFc in 15 adults. To allow for direct comparison between products, all patients received the Alprolix standard 50 IU/kg dose.

INDICATIONS AND USAGE

What is Rebinyn® Coagulation Factor IX (Recombinant), GlycoPEGylated?

Rebinyn® is an injectable medicine used to replace clotting Factor IX that is missing in patients with hemophilia B. Rebinyn® is used to treat and control bleeding in people with hemophilia B. Your healthcare provider may give you Rebinyn® when you have surgery. Rebinyn® is not used for routine prophylaxis or for immune tolerance therapy.

IMPORTANT SAFETY INFORMATION

What is the most important information I need to know about Rebinyn®?

- **Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia treatment center.** Carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing Rebinyn®.

Who should not use Rebinyn®?

Do not use Rebinyn® if you:

- are allergic to Factor IX or any of the other ingredients of Rebinyn®.
- are allergic to hamster proteins.

What should I tell my health care provider before using Rebinyn®?

Tell your health care provider if you:

- have or have had any medical conditions.
- take any medicines, including non-prescription medicines and dietary supplements.
- are nursing, pregnant, or plan to become pregnant.
- have been told you have inhibitors to Factor IX.

How should I use Rebinyn®?

- Rebinyn® is given as an infusion into the vein.
- **Call your healthcare provider right away if your bleeding does not stop after taking Rebinyn®.**
- Do not stop using Rebinyn® without consulting your healthcare provider.

What are the possible side effects of Rebinyn®?

- **Common side effects include** swelling, pain, rash or redness at the location of the infusion, and itching.
- **Call your healthcare provider right away or get emergency treatment right away if you get any of the following signs of an allergic reaction:** hives, chest tightness, wheezing, difficulty breathing, and/or swelling of the face.
- **Tell your healthcare provider about any side effect that bothers you or that does not go away.**
- Animals given repeat doses of Rebinyn® showed Polyethylene Glycol (PEG) inside cells lining blood vessels in the choroid plexus, which makes the fluid that cushions the brain. The potential human implications of these animal tests are unknown.

Please see Brief Summary of Prescribing Information on the following page.

Rebinyn® is a prescription medication.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Learn more at rebinyn.com and connect with your local HCL

novo nordisk®

Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, New Jersey 08536 U.S.A.

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rebinyn®
Coagulation Factor IX (Recombinant), GlycoPEGylated

rebinyn®

Coagulation Factor IX (Recombinant), GlycoPEGylated

Brief Summary Information about:
REBINYN® Coagulation Factor IX (Recombinant), GlycoPEGylated

Rx Only

This information is not comprehensive.

- Talk to your healthcare provider or pharmacist
- Visit www.novo-pi.com/REBINYN.pdf to obtain FDA-approved product labeling
- Call 1-844-REB-INYN

Read the Patient Product Information and the Instructions For Use that come with REBINYN® before you start taking this medicine and each time you get a refill. There may be new information.

This Patient Product Information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have questions about REBINYN® after reading this information, ask your healthcare provider.

What is the most important information I need to know about REBINYN®?

Do not attempt to do an infusion yourself unless you have been taught how by your healthcare provider or hemophilia treatment center.

You must carefully follow your healthcare provider's instructions regarding the dose and schedule for infusing REBINYN® so that your treatment will work best for you.

What is REBINYN®?

REBINYN® is an injectable medicine used to replace clotting Factor IX that is missing in patients with hemophilia B. Hemophilia B is an inherited bleeding disorder in all age groups that prevents blood from clotting normally.

REBINYN® is used to treat and control bleeding in people with hemophilia B.

Your healthcare provider may give you REBINYN® when you have surgery.

REBINYN® is not used for routine prophylaxis or for immune tolerance therapy.

Who should not use REBINYN®?

You should not use REBINYN® if you

- are allergic to Factor IX or any of the other ingredients of REBINYN®
- if you are allergic to hamster proteins

If you are not sure, talk to your healthcare provider before using this medicine.

Tell your healthcare provider if you are pregnant or nursing because REBINYN® might not be right for you.

What should I tell my healthcare provider before I use REBINYN®?

You should tell your healthcare provider if you

- Have or have had any medical conditions.
- Take any medicines, including non-prescription medicines and dietary supplements.
- Are nursing.
- Are pregnant or planning to become pregnant.
- Have been told that you have inhibitors to Factor IX.

How should I use REBINYN®?

Treatment with REBINYN® should be started by a healthcare provider who is experienced in the care of patients with hemophilia B.

REBINYN® is given as an infusion into the vein.

You may infuse REBINYN® at a hemophilia treatment center, at your healthcare provider's office or in your home. You should be trained on how to do infusions by your hemophilia treatment center or healthcare provider. Many people with hemophilia B learn to infuse the medicine by themselves or with the help of a family member.

Your healthcare provider will tell you how much REBINYN® to use based on your weight, the severity of your hemophilia B, and where you are bleeding. Your dose will be calculated in international units, IU.

Call your healthcare provider right away if your bleeding does not stop after taking REBINYN®.

If your bleeding is not adequately controlled, it could be due to the development of Factor IX inhibitors. This should be checked by your healthcare provider. You might need a higher dose of REBINYN® or even a different product to control bleeding. Do not increase the total dose of REBINYN® to control your bleeding without consulting your healthcare provider.

Use in children

REBINYN® can be used in children. Your healthcare provider will decide the dose of REBINYN® you will receive.

If you forget to use REBINYN®

If you forget a dose, infuse the missed dose when you discover the mistake. Do not infuse a double dose to make up for a forgotten dose. Proceed with the next infusions as scheduled and continue as advised by your healthcare provider.

If you stop using REBINYN®

Do not stop using REBINYN® without consulting your healthcare provider.

If you have any further questions on the use of this product, ask your healthcare provider.

What if I take too much REBINYN®?

Always take REBINYN® exactly as your healthcare provider has told you. You should check with your healthcare provider if you are not sure. If you infuse more REBINYN® than recommended, tell your healthcare provider as soon as possible.

What are the possible side effects of REBINYN®?

Common Side Effects Include:

- swelling, pain, rash or redness at the location of infusion
- itching

Other Possible Side Effects:

You could have an allergic reaction to coagulation Factor IX products. **Call your healthcare provider right away or get emergency treatment right away if you get any of the following signs of an allergic reaction:** hives, chest tightness, wheezing, difficulty breathing, and/or swelling of the face.

Your body can also make antibodies called "inhibitors" against REBINYN®, which may stop REBINYN® from working properly. Your healthcare provider may need to test your blood for inhibitors from time to time.

You may be at an increased risk of forming blood clots in your body, especially if you have risk factors for developing blood clots. Call your healthcare provider if you have chest pain, difficulty breathing, leg tenderness or swelling.

Animals given repeat doses of REBINYN® showed Polyethylene Glycol (PEG) inside cells lining blood vessels in the choroid plexus, which makes the fluid that cushions the brain. The potential human implications of these animal tests are unknown.

These are not all of the possible side effects from REBINYN®. Ask your healthcare provider for more information. You are encouraged to report side effects to FDA at 1-800-FDA-1088.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

What are the REBINYN® dosage strengths?

REBINYN® comes in three different dosage strengths. The actual number of international units (IU) of Factor IX in the vial will be imprinted on the label and on the box. The three different strengths are as follows:

Cap Color Indicator	Nominal Strength
Red	500 IU per vial
Green	1000 IU per vial
Yellow	2000 IU per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

How should I store REBINYN®?

Prior to Reconstitution (mixing the dry powder in the vial with the diluent):

Store in original package in order to protect from light. Do not freeze REBINYN®.

REBINYN® vials can be stored in the refrigerator (36-46°F [2°C-8°C]) for up to 24 months until the expiration date, or at room temperature (up to 86°F [30°C]) for a single period not more than 6 months.

If you choose to store REBINYN® at room temperature:

- Note the date that the product is removed from refrigeration on the box.
- The total time of storage at room temperature should not be more than 6 months. Do not return the product to the refrigerator.
- Do not use after 6 months from this date or the expiration date listed on the vial, whichever is earlier.

Do not use this medicine after the expiration date which is on the outer carton and the vial. The expiration date refers to the last day of that month.

After Reconstitution:

The reconstituted (the final product once the powder is mixed with the diluent) REBINYN® should appear clear without visible particles.

The reconstituted REBINYN® should be used immediately.

If you cannot use the reconstituted REBINYN® immediately, it should be used within 4 hours when stored at or below 86°F (30°C). Store the reconstituted product in the vial.

Keep this medicine out of the sight and out of reach of children.

What else should I know about REBINYN® and hemophilia B?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use REBINYN® for a condition for which it is not prescribed. Do not share REBINYN® with other people, even if they have the same symptoms that you have.

More detailed information is available upon request.

Available by prescription only.

For more information about REBINYN®, please call Novo Nordisk at 1-844-REB-INYN.

Revised: 11/2017

REBINYN® is a trademark of Novo Nordisk A/S.

For Patent Information, refer to: http://novonordisk-us.com/patients/products/product-patents.html

Manufactured by:
Novo Nordisk A/S
Novo Allé, DK-2880 Bagsværd, Denmark

For information about REBINYN® contact:
Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536, USA

USA17BIO03951 12/2017

novo nordisk®

"One of the most important things you can do on this earth is to let people know they are not alone."

— Shannon L. Alder

BCares

THE COALITION FOR HEMOPHILIA B PATIENT ASSISTANCE PROGRAM

The high cost of medical care is often a challenge for people with hemophilia B. Fortunately, insurance coverage, government programs and other forms of patient assistance cover much of that cost. Unfortunately, these programs do not cover the cost of non-medical emergencies, which may interfere with a family or individual's ability to deal with day-to-day life with a bleeding disorder. These emergencies may involve struggling to having enough resources for housing, food, transportation, or a range of other necessary and critical needs.

When these needs are not met, the health and well-being of the patient as well as the entire family can be negatively affected. Often, assisting a person in an immediate circumstance is all that's needed to keep the situation from spiraling out of control.

The Coalition for Hemophilia B deeply cares about families and individuals, and the urgent needs they may face. Several years ago, because of this and in order to live true to our mission statement, we established a patient assistance program for hemophilia B patients and families. We reintroduce our program as ***BCares.***

BCares operates with funding generously donated by pharmaceutical manufacturers, homecare companies, business partners, and other interested supporters.

Those donating share our belief - in the case of an urgent situation, we can all do more to help. It is our obligation as a community to lend a hand and assist those in short-term, dire straits.

The Coalition for Hemophilia B is able to offer a limited amount of financial aid to our factor 9 community members who face a financial emergency. Those requesting assistance can submit a simple, confidential application. Each application will be reviewed thoroughly by a committee, who will determine and prioritize grants based on the request and level of urgency.

How you can help: We are exceedingly grateful to the donors whose charity and compassion have made this critical program possible. Please consider becoming involved by offering additional funds so we may help more hemophilia B patients through challenging times.

For more information, please contact:

Farrah Muratovic
farrahm@hemob.org
The Coalition for Hemophilia B

Tel: 212•520•8272
hemob.org

TREATMENT NEWS

BY DR. DAVID CLARK

Rebinyn and COVID-19

Novo Nordisk has sent a letter to healthcare professionals warning them that Rebinyn, their factor IX product, can interfere with some of the clotting assays used to monitor COVID-19 disease progression in patients. We have seen that many COVID-19 patients develop thrombosis. Thrombosis is the formation of a clot (a thrombus) inside a blood vessel. It is a dangerous condition because not only can the clot cut off blood flow in that vessel, it can also break loose and travel to other parts of the body. A thrombus that breaks loose is called an embolism. If the embolism gets stuck in a major organ and blocks blood flow there, it can cause significant damage, even death. The conditions, which are called thromboembolic complications, can result in various disorders such as deep vein thrombosis (DVT), disseminated intravascular coagulation (DIC), pulmonary embolism (PE) and/or strokes (embolism in the brain).

The COVID patients who develop thromboembolic complications are treated with anticoagulants, like heparin, that must be dosed based on the results of clotting assays. Rebinyn interferes with some of these clotting assays that doctors are relying on to provide safe treatment. Other hemophilia treatment products may also affect these assays, but so far, Novo is the only company that we've heard from. (On the hemophilia A side, Roche/Genentech reports that Hemlibra also interferes with some clotting assays.)

Another article in this newsletter discusses hemophilia and COVID-19. One of its major recommendations is to involve your hemophilia treatment center (HTC) or hematologist if you are being treated for COVID-19. This is one of the reasons most physicians don't know much about hemophilia, and they know even less about the products we use. We also know very little about COVID-19 and its treatment. You can at least solve the problem of little hemophilia-related knowledge by involving your treater. Also, make everyone aware if you have been in any kind of clinical study for anything. Don't just think that it doesn't involve hemophilia and/or COVID. We keep finding that COVID affects a lot more than we know.

Please don't stop taking your factor, whether it's Rebinyn or another product. That can only make things worse. Just get the help you need.

[You can read the Novo Nordisk warning letter from 5/18/20 in the COVID-19 Resources section of our website at www.hemob.org (https://bit.ly/2zy1rlf).]

ApcinteX Begins Phase Ib Study of SerpinPC in Hemophilia Patients

ApcinteX, a biotech company spun off from the University of Cambridge in England, is developing SerpinPC for treatment of hemophilia A and B patients, with or without inhibitors. The product is an inhibitor of activated protein C (APC), an anticoagulant. It is expected to be dosed subcutaneously once a month. Inhibiting APC has been shown in animal studies to restore the balance in the clotting system to provide normal clotting. After a successful Phase Ia study in healthy volunteers without hemophilia, the company is beginning a Phase Ib study in subjects with hemophilia. In addition to looking at safety, the main subject of Phase I studies, the Phase Ib study will also look at pharmacokinetics as well as any reduction in bleeding episodes that might occur at low doses of the product. [ApcinteX press release, 3/17/20]

Aptevo Treats First Pediatric Patient with IXINITY

The manufacturer of IXINITY factor IX concentrate, Aptevo Therapeutics (now Medexus—see below), announced that it has treated the first patient in a Phase IV study aimed at obtaining a pediatric indication for the product. Phase IV studies are done after a product has already been licensed. They are most often done either to extend an indication, as is the case here, or to answer concerns that the Food and Drug Administration (FDA) might have about a licensed product. IXINITY was licensed in 2015, only for patients 12 years of age and older. The company is hoping to expand that to kids under age 12 with this study. We know that younger children's bodies process factor IX slightly differently than adults, so the FDA requires proof of how a product works for that age group. According to the World Federation of Hemophilia, approximately 34% of patients were under age 12 in 2017. [Aptevo press release, 1/30/20]

Aptevo Sells IXINITY to Medexus

Medexus Pharmaceuticals, Inc., a US/Canadian company, purchased worldwide rights to IXINITY from Aptevo for approximately $30 million. Medexus will continue the pediatric Phase IV study described above. [Medexus press release, 2/28/20]

Bayer Halts Phase II Study of Anti-TFPI Treatment

Bayer has been developing BAY-1093884, an inhibitor of tissue factor pathway inhibitor (TFPI). TFPI is an anticoagulant that helps to control the clotting process. Laboratory and animal studies have suggested that

inhibiting TFPI might be an effective way to restore the balance in the clotting system to control bleeding in patients with hemophilia A or B, with or without inhibitors. A Phase I study in humans showed no obvious safety issues; however, in the Phase II study at higher doses three subjects developed thrombosis (dangerous internal clotting). Bayer has therefore stopped the studies.

Novo Nordisk (see report below) has also stopped studies of its anti-TFPI treatment because of thrombosis. It could be that inhibiting TFPI requires more sensitive control than can be achieved by these methods. This has been a popular approach, with Pfizer, Takeda, and GC Pharma also developing anti-TFPI products. We'll see whether they have any better success.

Products targeting other anticoagulants, such as antithrombin, protein C, and protein S, are also being developed. Some of these may prove more effective. [EAHAD abstract P099, 2/7/20. Abstracts (summaries) from the European Association for Haemophilia and Allied Disorders (EAHAD) 2020 Congress can be found, free of charge, through their website at http://eahad.org/]

Bayer Reports on PEG from EHL Product

The extended half-life (EHL) hemophilia B product Rebinyn from Novo Nordisk uses polyethylene glycol (PEG) chains attached to the factor IX molecule to keep it in circulation longer. Rebinyn appears to be as safe as the other EHL products, but there has been a lingering question whether the PEG could cause trouble with long-term use. Bayer presented data from studies of its hemophilia A product JIVI, which also uses PEG to extend the half-life. Bayer looked at 120 adults/adolescents and 59 children (<12 years) who had been treated with JIVI for up to five years. The company found that it took about a year to reach a steady-state (constant) level of PEG in their plasma and about 2.5 years in their kidneys. The PEG levels were all low, mostly just at the lower detection limit of the assay. No adverse effects and no signs of kidney damage were observed. This provides some additional evidence that PEG-containing products are safe. [EAHAD abstract P049, 2/7/20]

California Group Developing an Oral Factor IX Concentrate

A group of California researchers is developing an oral version of factor IX for treatment of hemophilia B. They found that a recombinant factor IX fused to transferrin, a normal human protein that transports iron around the body, has increased oral bioavailability (i.e., ability to enter the blood stream when taken by mouth). Previous studies have shown that transferrin can also help to transport protein drugs across epithelial cell membranes, which include the inner linings of the intestines. In hemophilic mice, the researchers showed that oral delivery of the factor IX fusion protein gave comparable results to those for a commercial intravenous factor IX product. The researchers are currently in an early stage of development. [Xie et al., International Journal of Molecular Sciences, 21(1), 21, 2020; originally published 12/18/19]

Catalyst Completes Phase IIb Study of Sub-Q Variant Factor IX

Catalyst Biosciences has completed dosing and follow-up for its Phase IIB clinical study of dalcinonacog alfa (DalcA). DalcA is a variant factor IX with a higher potency and extended half-life, given by subcutaneous injection. Six subjects with severe hemophilia B were treated with a single intravenous dose of DalcA, followed by daily sub-Q doses for 28 days. The subjects achieved steady-state factor IX levels of 14–28% with zero bleeds. The product was well-tolerated and no inhibitor development was seen. The half-life of DalcA ranged from 84 to 112 hours. The extended half-life may allow less frequent dosing once a steady-state level is achieved. [Catalyst press release, 4/21/20]

Catalyst Developing DalcA-Based Gene Therapy

Catalyst is using DalcA in a next-generation gene therapy product under development. Using a novel high-transducing (more active in introducing the DalcA gene into cells) AAV vector licensed from Stanford University, Catalyst has shown good results in hemophilia B mice. The novel vector led to approximately 10-fold higher factor IX levels than previous AAV vectors. [EAHAD abstract P030, 2/7/20]

Catalyst Receives European Patent for DalcA Portfolio

Catalyst has received a European patent for its DalcA portfolio of factor IX variants for use in both replacement therapy and gene therapy. The company now has broad patent coverage in the US, EU, Japan, and China. [Catalyst press release, 4/28/20]

Catalyst Announces Phase III Study Design for Inhibitor Treatment

Catalyst Biosciences is developing marzeptacog alfa (activated) (MarzAA) for treatment of hemophilia patients with inhibitors. MarzAA is a subcutaneous (sub-Q) variant FVIIa with a longer half-life and higher activity than normal FVIIa. The company presented data showing that MarzAA could quickly (< 20 min) reduce bleeding in hemophilia A mice. It also presented promising results from a Phase I study of safety, pharmacokinetics, and pharmacodynamics. With input from the FDA and the European Medicines Agency, Catalyst is designing a Phase III study to test MarzAA in 75 hemophilia A and B patients with inhibitors. The study is expected to start later this year, depending on developments with the COVID-19 pandemic. [EAHAD abstracts P036 and P128, 2/7/20; Catalyst press release, 4/6/20]

TREATMENT NEWS

CSL: Up to 21-Day Dosing Intervals Possible with Idelvion

An international study of CSL Behring's Idelvion has shown that it can adequately control bleeding with dosage intervals of up to 21 days in some patients. The study looked at 59 patients (FIX ≤ 2%) receiving Idelvion at 7-day (dose 35–50 IU/kg), 10- or 14-day (50–75 IU/kg) and 21–day (100 IU/kg) dosing intervals. The 21-day group consisted of patients whose bleeding had been well-controlled with 14-day dosing for at least six months.

Average steady-state trough levels ranged from 22% of normal with 7-day dosing to 7.6% with 21-day dosing. Median annualized bleeding rates (ABRs) were zero, 0.28, 0.37, and zero for the 7-, 10-, 14-, and 21-day regimens, respectively. Treatment was well tolerated and there were no inhibitors. This shows that some patients may be fine with 21-day dosing intervals. [ME Mancuso et al., Journal of Thrombosis and Haemostasis, Epub ahead of print, 2/20/20]

Dyno Looks at AAV Design

Dyno Therapeutics, a new spin-off from Harvard Medical School, is looking at ways to improve the adeno-associated viruses (AAVs) being used for gene therapy. Using machine learning (artificial intelligence), the company looked at all possible mutations of AAV2 to see what changes would alter immunogenicity (activating the immune system against it), stability, ability to multiply, and distribution to different tissues in the body. Interestingly, Dyno also discovered a previously unknown gene in AAV. This work may lead to better AAVs for gene therapy. [Ogden et al., Science, 366(6469) 11391143, 2019]

Freeline Gene Therapy Development Update

Freeline Therapeutics, a gene therapy spin-off from University College London, is developing FLT180a, a gene therapy for hemophilia B. In recent announcements, the company reported that the first two patients in its Phase I/II clinical study have factor IX levels that have remained steady at about 40% through 66 and 74 weeks. The company continues to enroll patients and expects to release additional results later this year. [Freeline press releases, 12/19/19 and 2/7/20]

LFB/HEMA Receives FDA Approval for Sevenfact for Inhibitor Treatment

The FDA has approved Sevenfact, a recombinant activated factor VII (FVIIa) product, for treatment of hemophilia A and B patients with inhibitors. Sevenfact is produced by Laboratoire Francais du Fractionnement et des Biotechnologies, SA (LFB), a French biotech and plasma fractionation company. It will be distributed in the United States by HEMA Biologics. The product is manufactured in the milk of transgenic rabbits – rabbits that have been genetically engineered to produce human factor VII in their milk. The transgenic approach has already been used in other FDA-licensed products. Because of the large amount of factor VII that can be obtained, transgenic production has the promise to decrease production costs. Sevenfact is expected to have similar properties to the other FVIIa product, NovoSeven, that is already on the market. There has been no word on when it will be available. [FDA press release, 4/1/20]

Novo Stops Clinical Studies of Concizumab

Novo Nordisk has been developing concizumab, a monoclonal antibody that binds to the anticoagulant protein Tissue Factor Pathway Inhibitor (TFPI) and prevents it from slowing the clotting process. Concizumab and several other treatments are being developed to increase the ability of hemophilia patients' blood to clot by inhibiting various anticoagulants (inhibiting the inhibitors). The product is expected to work in patients with either hemophilia A or B, with or without inhibitors. Concizumab was in a Phase II study and two Phase III studies. Three of the Phase III patients developed non-fatal thrombotic events (dangerous internal clotting). Novo has now stopped all three studies while it investigates the problem and works with the FDA and others to decide the best way to move forward. [Novo Nordisk press release, 3/16/20]

Pfizer Reports One-Year Data for Gene Therapy

Pfizer has taken over development of fidanacogene elaparvovec, a gene therapy for hemophilia B that was originally invented by Spark Therapeutics as SPK-9001. Pfizer is currently conducting a Phase III study of the product. At EAHAD, the company presented health-related quality of life (HRQoL) data from 15 patients at least one year after treatment. The patients had medians of zero bleeds (range 0–4) and zero factor infusions (range 0–10). Using validated questionnaires, Pfizer researchers found that all of the patients had meaningful improvements in HRQoL. [EAHAD abstract P192, 12/8/19]

Sanofi vs. CSL in Court

Bioverativ, a part of Sanofi, filed suit against CSL Behring on March 4, 2020, claiming that CSL's product Idelvion, an extended half-life (EHL) factor IX, infringed several Bioverativ patents. Bioverativ/Sanofi makes Alprolix, another EHL factor IX product. On April 15, the U.S. District Court of Delaware ruled that there was no willful infringement. The court found that CSL's close monitoring of Bioverativ's development activities for Alprolix are considered standard within the pharmaceutical industry. [Life Sciences Intellectual Property Preview article, 3/5/20; JD Supra article, 4/15/20]

Takeda Reports Animal Data for TAK-748 Gene Therapy

Takeda is developing a second-generation gene therapy for hemophilia B called TAK-748. It includes a stronger

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promoter to increase production of factor IX by the transduced (modified by the new gene) liver cells. (Genes include regulatory elements, including promoters, that control how much of the gene product is produced.) It also uses the Padua factor IX variant that has a higher clotting activity. In pre-clinical studies in mice and rhesus monkeys, Takeda found dose-dependent (the factor IX level increases with increasing AAV vector dose) factor IX increases and no safety issues. The results allowed the company to estimate the required dose for human studies. [EAHAD abstracts P038 and P149, 2/7/20]

Takeda has also entered into a long-term research alliance with Evotec, a German biotech company. The companies will establish a 20-person gene therapy team in Austria, where Takeda owns a gene therapy facility it inherited from Shire. [Evotec press release, 4/6/20]

uniQure Completes Gene Therapy Trial Treatment

uniQure announced that it has completed enrollment and dosing for its Phase III study of AMT-061, the company's gene therapy for hemophilia B. Fifty-four subjects have been treated, exceeding the initial target of 50 patients. The company expects to have results by the end of 2020 and file a license application with the FDA in 2021. [uniQure press release, 3/26/20]

uniQure Reports One-Year Data from Phase IIb Study of Gene Therapy AMT-061

uniQure is developing AMT-061, a gene therapy treatment for hemophilia B. The company's previous treatment, AMT-060, is the same as AMT-061, except that uniQure switched from a wild-type factor IX gene in AMT-060 to the Padua factor IX gene variant for AMT-061. The Padua variant exhibits a much higher activity than the wild-type gene. The Phase IIb study was conducted as a bridge between the two products, showing that AMT-061 has the same safety profile as AMT-060 but with higher factor IX levels in the treated subjects. The three subjects in the study developed an average factor IX level of 45% (30%, 51%, and 54%, individually). At one year after treatment, the subjects had no safety issues, no bleeds, and required no additional factor infusions (except for one patient who had a preplanned hip replacement and was treated with standard factor IX for the procedure). There was no sign of inhibitor development, and none of the subjects were treated with corticosteroids. Note that all three subjects had preexisting antibodies against the AAV5 vector but were treated successfully anyway. [EAHAD abstract OR10, 2/7/20]

uniQure Presents Data on Long-Term Expression after Dosing Young Mice

One of the issues in hemophilia gene therapy is that the effect of the treatments may not last when given to children. By design, the new factor IX genes introduced into liver cells do not integrate themselves onto the chromosomes with the rest of the cell's genes (the genome). The new genes remain as separate pieces of DNA in the cell nucleus. The separate genes are called exosomes. Until now, it was thought that the exosomes would be lost when the liver cells divide as the liver grows. Because of this, it was assumed that treating young children, who have rapidly growing livers, would be pointless because they would soon lose the new gene. uniQure recently presented results from a study in young mice that raises questions about that assumption. The study showed that mice treated as early as two days old with the AMT-060 AAV5 vector appeared to maintain factor IX expression for up to 1.5 years, their average life span. That provides some confidence that young children with hemophilia B might be able to be treated after all. Note this remains to be proven in humans.

Other companies are approaching the treatment of children by developing methods to integrate the new genes into specific locations on the chromosomes. The problem is that if you let the new gene insert itself into random locations on the chromosomes, it can disrupt other genes, which can lead to cancer and other disorders. Some companies are developing gene therapies that insert the new gene into specific locations on the chromosomes, which they know are safe. [uniQure press release and presentation slides, 5/14/20]

uniQure Reports Patient Experiences with Gene Therapy

Investigators in Germany reported on the experiences of three patients who received uniQure's AMT-060 gene therapy for hemophilia B. The three patients were treated in uniQure's Phase I/II study and have shown stable factor IX expression for 3.5 years with levels of 5.1–7.5%. All three patients have become more active and participate more in sports. They all expressed anxiety about how long the higher factor levels would last. None of them expressed concern about long-term negative consequences of the treatment. The article is available for free on the journal website and is easy to read. [Miesbach and Klamroth, Patient Preference and Adherence, 14:767–770, 2020]

CSL Licenses uniQure's Gene Therapy for Hemophilia B

6/24/20 CSL Behring and uniQure announced that CSL has obtained worldwide rights to commercialize uniQure's AMT-061 (etranacogene dezaparvovec) gene therapy for hemophilia B. AMT-061 consists of an AAV-5 viral vector carrying the higher-activity Padua variant factor IX gene. It is currently in Phase III clinical studies where it has shown excellent results with minimal adverse reactions. The agreement leverages CSL's strong global presence in hemophilia B. CSL already has a growing gene therapy capability with development projects for sickle cell disease and primary immunodeficiency diseases.

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TEAM VOLUNTEER TRAINING WEEKEND

BY ROCKY WILLIAMS, GLENN MONES AND KAREN BROGNO

Over the March gala weekend, we arranged two full days of training in New York for our Coalition team members and our amazing dedicated volunteers. It was a fantastic opportunity to spend meaningful time together, have fun, learn new skills, and prepare for future events.

We were honored to have Lee Kim from Design Dream Labs participate. She facilitated an exercise called, *Memory Kaleidoscope* where we used images that resonated with individuals. With each piece of artwork, we expressed our feelings and thoughts. This opened the group up to sharing and everyone learned new storytelling techniques for bringing communities together.

The Coalition for Hemophilia B Core Team also participated in a special training in *Mental Health First Aid*. The training is designed to teach participants how to recognize when someone is struggling emotionally, how to have an effective conversation about it and where to turn for help. Among the key takeaways were how to recognize the signs and symptoms of common mental health conditions, a five-step action plan on how to respond to someone experiencing psychological distress, where to guide others for mental health information and care, suicide prevention, and how to respond to an opioid overdose.

The course was led by Debbie de la Riva. Debbie is a licensed counselor with a master's degree in Counseling Psychology from the University of Houston. She is also a hemophilia mom with a long record of service to the community. Debbie is conducting mental health training throughout the country. All of the participants received a *Certificate of Completion, Mental Health First Aid*.

The training was concluded with sessions led by Rocky Williams and Chris Villarreal. The sessions were focused on improving our skills as representatives of CHB. We participated in teamwork and teamplay activities that involved both cooperation and competition.

We discussed the details of how we work together as a team, each wearing many hats to ensure our programs are successful, educational, and fun!

HEMOPHILIA UPDATE

BY DR. DAVID CLARK

Joint Bleeding and Inflammation

Older research suggests that factor levels of 12–15% should protect hemophilia A and B patients from joint bleeding. Analysis of the levels of factor in the bloodstream is part of the field of pharmacokinetics (PK), which studies how drugs distribute themselves in the body. Measuring a patient's PK behavior with clotting factors is becoming an important part of hemophilia treatment as the products become more complex. Every patient is different, and physicians need to understand how each individual's body processes the factor in order to keep their factor levels in the safe range.

A group of U.S. and Canadian researchers studied 26 hemophilia patients (mostly severes, 21 As, 5 Bs) with joint damage (hemarthropathy) over two years to see how their joint damage correlated with their factor levels. They found no correlation with PK parameters, factor levels, or amount of time spent below the desired trough level in the days before a joint bleed!

What they found was that joint bleeding had more to do with the previous condition of the joints and the vascular remodeling (adding new blood vessels and rearranging existing ones) that occurs in the hemophilic joint. Rather than factor level, some of the results suggest that inflammatory flare-ups, like those seen in osteoarthritis, may trigger joint bleeds. This is an area that needs much more research.

For parents of young children diagnosed with hemophilia, this points up the benefit of starting them on prophylaxis early and keeping up with their infusions. The study shows that damaged joints tend to get worse, so it is important to keep the joints healthy from the beginning. [Zhou et al., Clinical and Applied Thrombosis/Hemostasis, 25:1–10, 2019]

A group from Argentina also suggests that inflammation may have a previously unknown role in joint damage. Inflammation is a part of the immune system's arsenal of tricks to fight off an infection or to take care of foreign material in the body. Immune system cells embedded in the tissues being attacked by infection or foreign material get activated and send out signals to the rest of the immune system that the tissue needs help. In the case of joint bleeding, it appears that iron from the red blood cells may be the trigger. Neither iron nor red blood cells are supposed to be in the synovial space, so they are seen as foreign material.

Neutrophils, which are a type of white blood cell that is part of the immune inflammatory response, are released into the synovial space to clean things up. Neutrophils release NETs (Neutrophil Extracellular Traps), which actually are like physical nets that catch the foreign material. NETs also trigger additional immune responses to clear away any damaged cells and to gobble up all of the foreign and cell debris. The researchers wondered whether NETs were involved in chronic (ongoing) joint damage.

In 23 hemophilia patients (22 As and 1 B) with chronic joint damage, the researchers did indeed find that the levels of NETs in the synovial fluid (the fluid surrounding a joint) correlated with the extent of joint damage as measured by the HJHS, a tool for evaluating joint damage in hemophilia. The persistence of NETs in the synovial fluid could also be a sign or cause of ongoing damage in the joint. The researchers also found that levels of NETs in the joints corresponded with levels of NETs in the bloodstream. Therefore, it may be possible to measure the NET levels in the blood to get an indication of what's going on in the joints. [EAHAD abstract P032, 2/7/20]

Interestingly, researchers are also looking at NETs in COVID-19. They have found that NETs are released in the bloodstream as a result of SARS-Cov-2 infection. Those NETs might be triggering the clotting complications seen in some COVID patients.

MASAC Issues Updated Emergency Room Guidelines

The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation (NHF) has issued updated guidelines for hospital emergency room (ER) treatment of patients with hemophilia and other bleeding disorders. MASAC Document #257 replaces Document #252. Receiving adequate care in an ER has always been a challenge for bleeding disorder patients. ERs often know little about hemophilia treatment. MASAC has updated its guideline with the latest treatment advice. The most important recommendation is to treat first before doing any diagnostic testing. The guideline states: "Treatment decisions should be based on the suspicion of a bleeding-related problem, not the documentation of one." It is recommended that hemophilia patients carry a copy of the guideline with them at all times to show to ER staff. [NHF website, 12/5/19: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/Guidelines-for-Emergency-Department-Management-of-Individuals-with-Hemophilia-and-Other-Bleeding-Disorders]

Inhibitors in Hemophilia B

The incidence of inhibitor development in hemophilia B has previously been estimated to affect only 3–5% of

patients. However, the PedNet study group, a primarily European organization of treaters who focus on children with hemophilia, published a study that suggests that the incidence is more like 10%. The study enrolled 154 previously untreated patients (PUPs) with severe hemophilia B who had been followed since birth in the PedNet study. None of the subjects had an inhibitor at the start of the study. Fourteen subjects developed inhibitors (seven high-titer) with an incidence of 9.3% after 75 exposure days and 10.2% after 500 exposure days. The type of product did not seem to be a factor, but this was a fairly small study. The study found allergic reactions in 4 (29%) of the patients who developed inhibitors during the study. It also looked at nonsense mutations and large gene deletions and found that they were strongly associated with the risk of inhibitor development. [Male et al., Haematologica, Epub ahead of print, 1/9/20]

Poor Joint Health Linked to Lower Self-Esteem in Adolescents

A study in Turkey looked at self-esteem among adolescent (age 13 to 19) hemophilia patients. Among 32 patients (28 As and 4 Bs; two-thirds with severe hemophilia; 81% on prophylaxis), the median Offer Self-Image Questionnaire (OSIQ) score was 212 compared to 250 for normal controls (35 healthy volunteers without hemophilia). Lower scores indicate less self-esteem. Their patients' Hemophilia Joint Health Scores (HJHS) were also lower than the controls, suggesting a correlation between self-esteem and joint condition. The authors propose that these tools, OSIQ and HJHS, may be useful for monitoring adolescent hemophilia patients. [Aydin Köker et al., Journal of Pediatric Hematology/Oncology, Epub ahead of print, 11/12/19]

Joint Condition May Improve with Treatment

We have usually assumed that once a joint is damaged, it does not get better. However, a study of hemophilia A patients using Hemlibra has shown that this assumption may not actually be true. Hemlibra is a substitute for factor VIII for hemophilia A patients. Using the Hemophilia Joint Health Score 2.1, researchers found that patients with target joints had significantly improved scores after 49 weeks on Hemlibra. Since Hemlibra is not known to have any other effect in the body besides clotting, it may be the reduction in joint bleeding that is causing improvements.

While this only applies to hemophilia A, it suggests that Bs could potentially see improvements in joint condition while on prophylaxis with factor IX. Further study is needed on whether higher, less variable factor IX levels might be more effective. [American Society of Hematology (ASH) 2019 abstract 626, 12/9/19]

Another study from Greece suggests that extended half-life (EHL) products could also improve joint condition. In 30 patients (21 As and 9 Bs) with severe hemophilia, EHL products improved their median HJHS scores from 31.5 (range 17–58) to 28.8 (14–54) over an average of 15.5 (6–26) months. This shows that prophylaxis with an EHL product can result in improved joint scores over time. [European Association for Haemophilia and Allied Disorders (EAHAD) abstract P053, 2/7/20]

More Issues with AAV Gene Therapy Vectors?

Adeno-associated viruses (AAVs) are being used as vectors to deliver new factor genes in all of the hemophilia A and B gene therapy treatments currently in clinical studies. One of the reasons that AAV was chosen was that it seemed to have a low immunogenicity (a low propensity to activate the immune system against it). AAV vectors have seemed to perform well in the current studies, but with inconsistent results and varying degrees of immune system reaction. For instance, BioMarin, which has recently submitted a license application for its hemophilia A gene therapy, has seen a decrease in factor VIII production over time in its clinical results. Gene therapy treatments for other diseases have shown similar declines for unknown reasons.

A recent review article surveyed 140 studies on AAV immunogenicity in laboratory studies. The study's authors found that despite the low immunogenicity of AAV itself, AAV gene therapy vectors can stimulate complex reactions in the immune system that can lead to attacks on the liver, the transduced liver cells (the cells that are modified with the new factor gene), and on the gene product (the "normal" factor VIII or IX that is produced by the new gene). The authors suggest that continued research is needed, and animal models that better reflect what is seen in humans should be developed. [Martino and Markusic, Molecular Therapy: Methods and Clinical Development, Epub ahead of print, 12/24/19]

ER Provider Education

Along with MASAC's updated emergency room guidelines (see the post above), Medscape, along with the American College of Emergency Physicians and the National Hemophilia Foundation (NHF), has set up a new education tool for ER providers. "Evaluation and Management of Hemophilia in the Emergency Department" is available through the NHF website. While it is intended for medical personnel, it is available to anyone and is free. [12/27/19, https://www.hemophilia.org/Newsroom/Medical-News/Medscape-Launches-Activity-for-Emergency-Department-Providers]

Green Park and NHF to Collaborate on Mental Health Initiative for Gene Therapy Patients

Green Park Collaborative (GPC) and the National Hemophilia Foundation (NHF) are partnering to develop a patient-reported outcome measurement (PROM) tool to look at the impact on the mental health of patients receiving gene therapy for hemophilia A and B. GPC is part of the Center for Medical Technology Policy (CMTP), a nonprofit organization dedicated to improving the quality, relevance, and efficiency of clinical research. Clinical research is research performed on human subjects, often in the development of new treatments.

This follows the coreHEM project, which defined the types of results that physicians and patients should expect out of gene therapy clinical studies. One of the expected outcomes was that companies would look at the emotional, psychological, and mental health aspects of a transformational treatment like gene therapy. There are currently no effective measurement tools available, so the partnership aims to develop one. [CMTP press release, 1/29/20]

Hematuria Is Frequent in Pediatric Hemophilia

A group from the Nationwide Children's Hospital in Columbus, Ohio, looked at hematuria (presence of blood in the urine) in pediatric hemophilia patients. Adults with hemophilia are known to have a higher prevalence of kidney disease, which can include hematuria, than the general population, but little is known about this condition in children with hemophilia. The study's authors found that 45% of the 93 patients surveyed (67 As and 26 Bs) had hematuria, and that older age and hemophilia A were associated with an increased likelihood of the disorder. With this high prevalence, the authors recommend the need for further study, including the impact on kidney function. [Davis et al., Haemophilia, 25(5): 782–788, 2019]

Five-Year MRI Joint Health Study

A group from the Netherlands studied joint damage over five years in 26 moderate and severe patients (age 12–29). Using both radiographs (X-rays) and magnetic resonance imaging (MRI), the researchers looked at changes in the joints over time. Radiographs are often used for diagnosis, but they can only detect later changes, which by then are mostly irreversible. The authors wanted to see whether MRI, which is regarded as the "gold standard" for joint imaging, could detect the early, often symptomless, changes that might predict further joint damage. They found that MRI could indeed predict future bleeding over a five-year time span by identifying even minor joint bleeding.

Early identification of joint bleeding can be used to start or intensify prophylaxis, emphasize adherence to treatment, or initiate treatment with anti-inflammatory drugs. The authors emphasize the need for early, aggressive therapy to forestall further damage.

MRI is limited by availability and cost, but the authors suggest that ultrasound may be a better alternative than radiography. Further research is needed to confirm associations between MRI and ultrasound in predicting joint damage. [Foppen et al., Blood Advances, Epub ahead of print, 1/9/20]

FDA Issues Revised Guidance on CJD in Blood and Plasma Products

Creutzfeldt-Jakob Disease (CJD) is a very rare, untreatable, and always fatal brain disease that is caused by abnormally folded proteins known as prions. It is related to other transmissible spongiform encephalopathies (TSEs) such as bovine spongiform encephalopathy (BSE, also known as "mad cow disease"). In the 1990s, BSE jumped from cows to humans, probably because of consumption of meat from cows infected with BSE, mainly in the United Kingdom. The human version of the BSE-related disease is called variant CJD or vCJD. With blood transfusion recipients and people with other disorders, including hemophilia, who used plasma-derived products potentially at risk, the Food and Drug Administration (FDA) issued strict guidelines for screening blood donors to prevent CJD and vCJD from entering the U.S. blood supply.

Now, with stricter controls in the meat industry to prevent contamination with BSE, the incidence of vCJD has dropped dramatically, and the FDA is slightly loosening its guidelines. There is no test for either CJD or vCJD, so donor screening recommendations have been used. Potential blood donors with any type of suspected TSE infection are still permanently deferred, along with any of their blood relatives. Until 1985, human growth hormone (HGH) was derived from human cadavers and was shown to transmit a form of CJD, so all HGH recipients were permanently deferred. Now, HGH is made recombinantly and is considered safe. Diabetics receiving bovine insulin were also deferred, but further experience has shown no evidence of transmission by bovine insulin, so those potential blood donors are now allowed. Some of the geographic restrictions covering people who have spent time in Europe and the UK have also been modified. The FDA believes that these changes will have no effect on the safety of the blood/plasma supply in the United States. [FDA website, draft January 2020, updated April 2020; https://www.fda.gov/media/124156/download]

Noninvasive Prenatal Diagnosis of Hemophilia

The presence of fetal cell-free DNA (fcfDNA, genes from the growing fetus in the mother's womb) in the mother's plasma was first reported in 1997. Now a group of Chinese researchers has reported that this fcfDNA can be used to determine whether the fetus carries mutations that would put it at risk for hemophilia and other disorders. Because the analysis is done on a simple blood sample taken from the mother, there is miniscule risk to either the mother or the child

So far, the test has only been used for two families at risk for hemophilia A but with good results, identifying one baby as not having hemophilia and one as being a carrier. The study needs to be repeated with a large patient group to finalize its validity. [Chen et al., BioTechniques, 68 (March 2020), Epub ahead of print]

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