NHF News Briefs

August 24 – 30, 2018

This report includes selected news items from the past week on issues of concern to the bleeding disorders community. It is designed to help keep NHF national and local leadership and staff informed of the latest information from the news media. It will be distributed by email on Thursday of each week, covering important news items from the previous seven days. Subjects covered will include hemophilia, other bleeding disorders, gene therapy, hepatitis, HIV/AIDS, and others.

Hemophilia of South Carolina
August 23, 2018

Government Officials, Medical & Policy Experts, and Patient Advocates Meet in Columbia for Bleeding Disorders Forum

Greenville, SC — On Thursday, August 16, and Friday, August 17, 2018, approximately 47 policy experts, government officials, medical professionals, and bleeding disorders advocates, met in Columbia, South Carolina, to address access to healthcare issues at a forum titled ***The South Carolina Challenge***, coordinated by Hemophilia of South Carolina (HSC) and their Advocacy Coalition.

The opening program, *Why Healthcare Matters,* featured testimony by HSC community member **Mr. Gene Wilson** about living with severe hemophilia and an inhibitor, as well as an opening keynote address by **Representative Leon Howard**, chair of the Medical, Military, Public and Municipal Affairs Committee in the South Carolina House of Representatives, who shared a bit about his families personal experiences regarding challenges to accessing healthcare and roadblocks he sees within the healthcare system, as well as his vision of how government can work to ensure persons with chronic diseases can have better and more reliable access to healthcare.

The next day, the program then featured a talk by Mr. Bryan Amick, deputy director of the Office of Health Programs at the South Carolina Department of Health and Human Services, who spoke about drug pricing issues in the state, incentivizing high quality care, policy solutions tailored to fit the competitive healthcare landscape, as well as an overview of the prospective solutions his office is seeking to provide better care for the more than 1 million Medicaid recipients in the state.

Ms. Renita Johnson, HSC board member and member of the Advocacy Coalition, then provided testimony regarding her family's experiences with bleeding disorders and the South Carolina Medicaid program. The forum then featured an open discussion of the challenges with access to care and treatment services, led by the three main hospital networks in the state.
\
The concluding portion of the afternoon program, *Access to Healthcare Part 2: Threats and Protections,* turned to a discussion of the existing instabilities in private and public healthcare plans and treatments, as well as programs that seek to mitigate these threats for bleeding disorders patients. Advocacy Coalition ambassador and HSC member Mr. Will Beaty, concluded the program with a testimony about the importance of such safety-net programs to the continuity of healthcare for people with chronic diseases.

The forum was a huge success and proved to be a useful conduit for bringing together the wide variety of expertise and experience from throughout the nation in order to share ideas and formulate solutions to the many challenges facing the South Carolina bleeding disorders community.

(NHF Note: This release has been excerpted from its original length. To view the story in its entirety, please visit this weblink: http://hemophiliasc.org/government-officials-medical-policy-experts-and-patient-advocates-meet-in-columbia-for-bleeding-disorders-forum/

Healio.com
August 24, 2018

Guidelines Intended to Accelerate Diagnosis, Improve Management of von Willebrand Disease

by Rob Volansky

(HemOnc Today) -- **Several organizations have collaborated to develop clinical practice guidelines for the diagnosis and management of von Willebrand disease**.

von Willebrand disease, the most common inherited bleeding disorder, affects 1% of people worldwide. Gynecologic manifestation is most common, causing heavy menstrual periods for women. Other symptoms range from nosebleeds to bleeding in joints.

However, diagnosis often is delayed due to lack of awareness.

"The complex clinical presentation of von Willebrand disease is a challenge for hematologists and referring physicians. Many patients remain undiagnosed until they experience a severe bleeding episode that could otherwise have been prevented," ASH President **Alexis A. Thompson, MD, MPH,** hematology section head and chair of childhood cancer and blood diseases at Ann & Robert H. Lurie Children's Hospital of Chicago, said in a press release.

That's why representatives of ASH, International Society on Thrombosis and Haemostasis, National Hemophilia Foundation, World Federation of Hemophilia and University of Kansas Medical Center agreed to collaborate. An international team of expert panelists, along with patient representatives, will develop evidenced-based guidelines that provide clear recommendations intended to ensure timely diagnosis and appropriate symptom management.

HemOnc Today spoke with **Paula James, MD, FRCPC,** professor and hematologist in the department of medicine at Queen's University in Kingston, Ontario, about the prevalence of von Willebrand disease, the reasons why awareness may be lacking, the need for clinical guidelines and how they may improve patient outcomes.

Question: Can you provide some background about von Willebrand disease?

Answer: von Willebrand Disease is the most common inherited bleeding disease, but there remains a lack of awareness or understanding among both the general public and physicians. Everyone has heard of hemophilia, but the magnitude of that disease is actually less than von

Willebrand disease. Men and women are affected equally in terms of inheritance of this disease, but clinicians generally end up diagnosing two or three women for every man. This is because one of the primary manifestations of this disease is heavy menstrual periods, along with bleeding after childbirth. However, there are a number of other symptoms and manifestations, including easy bruising, as well as bleeding from mucus membranes like the mouth and the gastrointestinal tract. Patients also may bleed after dental work or surgery, and nosebleeds are often a big problem in children. So there are a variety of symptoms. One of the reasons we started this guideline process is because a lot of challenges remain for patients in terms of disease recognition and diagnosis. The goal is to standardize the approach to improve patient access to diagnosis and, therefore, improve access to appropriate care.

Q: What constitutes appropriate care?

A: There are a number of management options for von Willebrand disease. If a woman has heavy menstrual periods, you have to think about gynecological treatments, which may include an oral contraceptive pill, an intrauterine device, or surgical procedures such as endometrial ablation or hysterectomy. There are medications to help prevent clot breakdown, such as tranexamic acid. Appropriate care also can include increasing plasma concentrations of von Willebrand factor through use of a medication called desmopressin. Another approach is to replace von Willebrand factor with human plasma-derived or recombinant concentrates. It is important to treat patients appropriately, and treatment needs to be individualized.

Q: Can you discuss outcomes?

A: Many of these patients are at risk for iron deficiency. Preventing and treating iron deficiency is a way to improve quality of life. For children with this disease, frequent nosebleeds interrupt class and can be scary for both children and teachers. Our focus is to look at quality-of-life parameters. In the most severe cases, if you bleed into muscles and joints, you can end up with bad arthritis.

Q: Why are clinical practice guidelines necessary for this disease?

A: The first reason is to clarify that it is more prevalent than hemophilia. Clinicians need to understand that these patients don't always get worked up properly. Doctors don't always recognize that the bleeding symptoms of these patients are abnormal when they seek medical attention. In particular, women with gynecological symptoms often are discounted. They are told it is normal to have heavy periods. Because of this, it can take up to 10 or 15 years for these

patients to get diagnosed. The goal of the guideline is to shorten that time. Although it is the most common inherited bleeding disorder, in terms of the general population, it is still quite rare. There could be more data and research about how to optimally treat these patients. As a result, we see variability from practice to practice in managing these patients. We are trying to address all of these issues.

Q: If this is the most common inherited bleeding disease, why is there still a lack of awareness about it among physicians?

A: In contrast to hemophilia, which we have known about for centuries, von Willebrand disease was only discovered in the early 1900s. There has been more recent research into the causes, but we are still learning about it. Another barrier to appropriate care is that the most common symptom is heavy menstrual bleeding. There remains some social stigma with discussing this openly. Because of that, patients don't always have a frame of reference for what is abnormal. We are trying to educate people that periods lasting more than 7 days are abnormal. Most people don't know that. Also, the lab work for this disease can be tricky. There are lot of layers to this.

Q: Who will serve as expert panelists?

A: There will be two panels. One will be focused on diagnosis, and the other will focus on management. ASH worked closely with the collaborating organizations. All four organizations nominated experts to be on the panels, and then ASH went through the process of vetting the nominations. The panels include a mix of hematologists, pediatricians and scientists. Importantly, we also have seven patient representatives who can speak to the reality of living with this disease. This includes four representatives on the diagnosis panel and three on the management panel.

Q: What will the guideline content cover?

A : In general, we are thinking about how to accurately diagnose and classify the disease, and how to respond to bleeding when it happens. We are thinking about how to prevent bleeding. We are thinking about the specific challenges for women. We are thinking about dealing with bleeding in surgical and dental situations, if patients need such a procedure.

Q: Is there a timeline for publication of the guidelines?

A: Some point in the next 2 years may be feasible — possibly by summer 2020.

For more information:

Paula James, MD, FRCP, can be reached at Queen's University, Room 2015, Etherington Hall, 94 Stuart St., Kingston, Ontario K7L 3N6; email: jamesp@queensu.ca.

Disclosure: *James reports conducting industry-funded research on von Willebrand factor pathobiology but not the diagnosis of von Willebrand disease. She reports no direct conflicts of interest with this guidelines project and has agreed to avoid direct conflicts — such as direct payments from industry — throughout the guideline development process.*

EMS World *(Emergency Medical Services)*
August 27, 2018

Blood Brothers

By Jolynn Tumolo

(Careers/Personnel)---In the fast-paced realm of EMS, a close-knit crew is invaluable. Deft communication through a word, even a glance, saves precious time and can mean all the difference for a patient in need. While the relationships of most teams are cemented through lengthy shifts and shared on-the-job experiences, **paramedic Cody Kunkel and EMT Brady Kunkel of Dodge Center, Minn.,** have a deeper well to draw from. They spent nearly two decades under the same roof as brothers.

"Growing up together and living in close quarters, you learn how to communicate early on or the ship doesn't float very well," says Cody, 23, a volunteer at Dodge Center Ambulance. "Communication is a huge strength for us because if, God forbid, we ever do have to get in the back of the rig with a critical patient, we can give each other a look or say a handful of words, and we instantly know everything the other person is thinking."

The two also have another bond shared by only about 20,000 other people in the United States: hemophilia. The brothers were diagnosed with severe hemophilia A before birth; an older brother, Jeff, was discovered to have the hereditary bleeding disorder as a baby.

"It's a disorder that prevents the blood from clotting normally. People with hemophilia are missing a specific protein in the clotting cascade. For us that specific protein is clotting factor VIII," explains Brady, 21, a full-time EMT at Dodge Center Ambulance. "Our bodies just never had the genetics to make the protein."

Childhood Medical Education

For the Kunkel brothers a childhood with hemophilia meant dozens of hospitalizations for internal bleeds or associated injuries at the Mayo Clinic in nearby Rochester. Most stays lasted just a few days, but more significant events, like a tear in the iliopsoas muscle, could take weeks to treat. When he was in middle school, Brady started hanging on to his old hospital bands. He's collected about 20 since then and displays them in his office.

"When you're stuck in a hospital bed as a child, at a very young age you're surrounded by all of these Latin and Greek medical terms—*hemophilia, hematoma*—and you don't really understand them," Brady recalls. "And you have two possible responses: You just want to get the hell out of there and go back to watching *Mickey Mouse Clubhouse,* or you want to know what they're talking about. I was the latter."

During extended stays Cody remembers visits to the Mayo One helicopter, where he got to meet the medical transport team and tour the craft. For the most part, the repeated hospitalizations didn't bother him, since it had been his whole life. But having to stay away from high-contact sports like football, hockey, and lacrosse frustrated both brothers.

While Cody and Brady may have felt hindered in their choice of extracurricular activities, they weren't coddled when it came to their condition. At just 5 years old, the boys took on the responsibility of self-administering injections of factor replacement therapy at home. They still routinely inject their factor product (usually right before a work shift), which significantly bumps up their clotting ability in the hours afterward. Injuries still pose a risk, however, of taking longer to clot and to heal, requiring more intensive treatment, or even doing long-term damage. Hemophilic arthropathy—joint damage caused by repeated bleeds—is common in people with hemophilia. Brady deals with such arthritis in his ankles, and Cody in his elbow. Both have undergone several surgeries to ease the pain.

In recent years Cody has prioritized getting to the gym for regular workouts in an attempt to boost his self-care.

"When I was growing up, there was a huge movement in the hemophilia world to keep these kids in bubbles: 'They shouldn't be out at the gym. They shouldn't be out playing sports. These kids are fragile,'" Cody says. "But now we're seeing studies coming out about people with hemophilia showing lower rates of injury if you are active and training your body to interact with its environment. Also, being active strengthens your muscles in your joints and lowers your risk of injury."

The Call of EMS

The brothers credit their firsthand exposure to the medical world with spurring them on to careers in healthcare. In fact, Cody was finishing up the prerequisites to get into nursing school when his younger brother announced plans to pursue EMT certification.

"My first thought was, *Whoa, that's a lot of work, dude. That's a lot of running around. We have hemophilia,*" Cody remembers. "I was concerned about his ankles, and I was absolutely concerned about future injuries."
Yet it was the very unpredictability of EMS that called to Brady.

"I think *wild* is the best word for it. You don't have the comforting feeling of being in a hospital, where you have hundreds of nurses and dozens of doctors and support staff behind you to assist with things," Brady says. "When you have a 9-1-1 call and things turn bad and the situation gets chaotic, it's a lot more challenging when it's just you and your partner and maybe a law-enforcement officer or a couple of firefighters. That's kind of what draws me: It's the challenge."

So Brady began studying for his EMT cert, with Cody helping as needed. Then, when Cody had a semester free before beginning nursing school, he decided to kill time by enrolling in the EMT program himself. He ended up loving the field too. And after both brothers earned their EMT certifications, Cody convinced Brady to volunteer with him at Dodge Center Ambulance.

Shortly afterward, paramedic Jared Oscarson came on board as ambulance director.

"When I arrived at Dodge Center Ambulance, Brady and Cody were new volunteer EMTs with the service. They had recently graduated from EMT class and were ready to help," says Oscarson. "Their compassion, empathy, and desire to learn was evident in all their work. These two jumped right into the operation, learning and growing."

Oscarson admits to being caught off guard when he learned they had hemophilia. He had never knowingly encountered anyone with the condition, so he sought more information.

“They talked openly and taught other staff members and me about hemophilia and what to do for them if they ever required care,” Oscarson says. “They manage their hemophilia with medications and care just like any other chronic disease and have a normal life. They are no different than anyone else in the department.”
Last year Brady took a full-time EMT position with the ambulance service, while Cody continued to volunteer and enrolled in paramedic school at the Mayo Clinic School of Health Sciences. He graduated and earned his paramedic credential in May.

No Looking Back

While Cody has accepted a full-time position as a paramedic an hour or so east in La Crosse, Wisc., he has every intention to continue as a volunteer EMT with his brother back in Dodge Center.

“As a volunteer EMT, my requirements aren’t too strenuous, so I’ll be able to go out there from time to time throughout the month and make it work,” Cody says. “Being able to be part of a volunteer EMS agency that gives back to a community that can’t necessarily afford the luxury of a full-time service is huge to me.”

Their two years of experience in EMS has taught the men one thing: Their career choice has not been a mistake. Neither Brady nor Cody has ever been seriously injured or felt limited on the job. Through life experience both have learned to quickly think things through before jumping in and to ask for help when needed to avoid injury.

“As kids, the doctors prevented us from doing a lot of stuff. I hated that, and I always had a little chip on my shoulder when I couldn’t do something because of my hemophilia,” says Brady. “I try not to let that affect me, especially when I want to be hardheaded and go beyond my bounds. At the end of the day I realize, if I get hurt, I can’t help anybody.”

Oscarson predicts bright futures for them both.

“I believe Brady and Cody have long careers ahead of them in EMS,” the ambulance director says, “and will continue to develop as leaders.”

Jolynn Tumolo is a freelance writer in Morgantown, Pa., and frequent contributor to EMS World.

HemophiliaFlorida.org
August 28, 2018

Hemophilia Foundation Awards $37,750 in Statewide Scholarships

Most Recipients Staying in State to Pursue Their Education Aspirations

The Hemophilia Foundation of Greater Florida (HFGF) is pleased to announce the distribution of $37,750 to 20 residents with bleeding disorders who are attending college this fall.

The Calvin Dawson Memorial Scholarship, named in honor of founder and first executive director of the HFGF, has been assisting those in the bleeding disorders community reach their higher education objectives for the past 20 years. Since the scholarship's inception, HFGF has granted more than $150,000 to worthy recipients.

"We are delighted to honor these 20 men and women who have aspirations to be the best they can be," says HFGF Executive Director Fran Haynes. "Ninety-one percent of all HFGF fundraising dollars go back to our bleeding disorders community, including our provision for annual scholarships of which we are quite proud."

HFGF scholarships are earmarked for Floridians with hemophilia, von Willebrand disease and other related hereditary bleeding disorders. Scholarships are attainable for high school graduates pursuing post-secondary education at a college, technical or trade school, or through other certification programs. Awards are based on merit, need, community service, and aspirations of the applicant as reflected in an essay.

Only two recipients are attending out-of-state schools—Vanderbilt and Syracuse—while the remainder, including Andrew Farren of St. Petersburg, remain in state.

"Receiving the HFGF scholarship means I am one step closer to achieving my dream of becoming a physician," says Andrew, now in his second year at St. Petersburg College with plans to transfer to the University of South Florida after receiving his Associate's Degree. "I'm thankful for the support this Foundation has given me and my family throughout the years, and I hope to someday inspire others like myself to pursue their aspirations."

For a complete list of scholarship recipients and the schools they will be attending, please visit http://www.hemophiliaflorida.org/scholarships.html

The Atlantic (magazine)
August 29, 2018

The Patients Who Don't Want to Be Cured

A hemophiliac says his genetic disorder is part of his identity, and therapies like CRISPR threaten to erase it.

By Sarah Zhang

(Science) --Jeff Johnson is 40 years old, and for all 40 of those years, he has been living with hemophilia. The genetic disorder prevents blood from properly clotting, which, if untreated, can cause uncontrollable bleeding. Yet, Johnson says, he does not want a cure. He grew up with hemophilia, went to summer camp with kids with hemophilia, and forged some of his closest relationships within the community.

I was interested in speaking to Johnson because new advances in gene therapy and gene editing are making the elusive cure seem closer than ever. At least five clinical trials are currently aiming to fix the faulty genes that underlie hemophilia. *The New York Times* recently interviewed patients from one gene-therapy trial who no longer had to worry about bruising and bleeding. "They Thought Hemophilia Was a 'Lifelong Thing,'" read the headline. "They May Be Wrong." It is unknown how long the effects of the therapy will last.

"I've been told the hemophilia cure is around the corner for literally the last 30 years," Johnson told me with a laugh. "Which I know sounds a little cynical, but when you've been around the bend as many times as I have, you kind of start hedging your bets." He does not speak for every hemophilia patient, of course, but at a time of increasing optimism about cures, his perspective is thought-provoking. Johnson lives in Washington State, and he is actively involved in the hemophilia-patient community. As is not uncommon for patients, he also works for a specialty pharmacy that dispenses hemophilia drugs.

In two conversations, we spoke about his experience growing up with hemophilia, his sense of identity, and his hopes for his newborn baby girl. *The interview has been lightly edited and condensed for clarity*.

Sarah Zhang: Tell me about your experience living with hemophilia.

Jeff Johnson: As early as I remember, honestly, I was having to go in to the emergency room for regular injections. I was on a different medication at the time, cryoprecipitate [which is derived from blood plasma and contains clotting factors]. I remember some kind of foggy memories as a toddler. The cryo was frozen, so it would have to sit out on the counter and thaw, and then they would do the infusion, and it would drip in over the course of a couple of hours.

There were people who were on clotting factor [which could be stored at home] when I was a kid. The hematologist had told my dad that factor might not be safe. There were hemophiliacs

getting sick from it, so my dad didn't let them use factor on me. It turns out hemophiliacs were getting sick because they were contracting HIV from their factor, so I was on the older treatment, but it ended up saving my life.

Right now, I deal more with the aftereffects of bleeds that I had years ago than I do with bleeds today. I had arthritis in my knees since my early 20s. I have arthritis and damage in my spine from bleeds, so those things just, they kind of wear on you more and more. I did get hepatitis, but I didn't get HIV.

Zhang: You've been talking about some of the challenges of living with hemophilia. So why are you personally not interested in a cure?

Johnson: The analogy I offer people, and I offer to you, is, as a woman, I'm sure you experience difficulties and challenges just being a woman in life. If someone came to you and said, "We've got a genetic cure for being a woman," that would be really bizarre to you because being a woman is who you are.

I am hemophilia. I don't have it. I am hemophilia. So when they come to me and say, "We've got a genetic cure for hemophilia," to me, that's just as weird as if you said you've got a genetic cure on the horizon for your left foot. This is really who I am. So I don't necessarily see it as something that needs a cure. As far as genetic cures go, the whole principle of changing my DNA is something I'm not comfortable with. A lot of us that grew up with it, it's part of our identity, so we don't really see separating our identity from us.

Zhang: Not everyone in the hemophilia community feels the same way about gene therapy or gene editing, of course. One thing I've heard talking to people with hemophilia is that for older folks—who grew up in the '70s and '80s when treatment was not as good and then lived through the HIV epidemic—there is a really strong sense of identity and community. Do you sense a generational divide in attitudes about a cure that would fundamentally alter your DNA?

Johnson: There is very much a generational divide. I think it's really more among parents.

Zhang: How so?

Johnson: The group I see most ardently wishing for a cure are new parents. They're people who don't have hemophilia, so it's not part of their identity, so they still kind of see it as something that's separate from us. To them, hemophilia is an invader—like for 20 years of their life where it wasn't part of their existence and they had a kid, and that kid had hemophilia. They see hemophilia as this intruder that needs to be cured and taken away from their lives.

Zhang: But if you're a kid with hemophilia, that's been part of you your whole life ...

Johnson: As you see parents and their families grow, you'll see a cure is all they talk about for the first four, five years. And then the kids get to like 5 to 10 and they're going to summer camp for kids with hemophilia and managing their disorder; the parents talk less and less about a cure.

And then when you get to the teenage years, unless they've got a really bad inhibitor or something [which prevents the use of clotting factors], the parents have kind of graduated on to, "It is what it is." If there's a cure, cool, but he's doing fine. You really see that in young parents because that cure is the light at the end of the tunnel that they didn't plan to be walking through.

Zhang: Do you have kids yourself?

Johnson: We have a two-month-old baby girl. My wife and I started talking about kids four years ago. I found out really late that I had contracted hepatitis from my cryo. Even though it's pretty safe to still conceive when you have hepatitis, it just was too nerve-racking to me to risk passing that infection on to my wife. So I fought for my insurance for three years to get treatment for my hepatitis. I switched jobs to the one I currently have, got new insurance, finally got approved. I actually finished my treatment regimen [last year].

Zhang: Did you think about the possibility of passing hemophilia to your kids?

Johnson: So the way that the genetics work, if I have sons, they'll inherit my Y chromosome. So if I only have sons, it wipes it out. If I have daughters, they're going to inherit my X. That's going to mean that either they carry it to their children, or it may present to the point where my daughter may actually have hemophilia.

Zhang: Does your daughter have symptoms of hemophilia?

Johnson: At two months, her body's still forming itself. So if we tested her factor level now, that would be meaningless because that would change in a few days. It really won't level out until she reaches puberty. We'll check her levels every now and then and if she grows up and she decides she wants to play soccer or something like that, it'll be something that we watch for, but we really won't know until she's a teenager if she's a full-fledged hemophiliac or if her factor levels are high enough that she's not going to be affected.
We've realized in the last 10 to 15 years that girls who we've traditionally called carriers, they're still bleeding from a factor deficiency sometimes. Not quite as badly as I do, but they're still bleeding. Treatment for girls with hemophilia is not as good as it is for boys with hemophilia. *(The doctor doesn't listen to her. But the media is starting to.)*

Zhang: How are girls treated differently?

Johnson: Hemophilia, growing up my entire life, because it's on the X chromosome, we were taught that it only affects boys. Only boys have hemophilia. And the big problem we're facing is that that is so entrenched in the medical establishment that hematologists will still tell women, "Well, you don't have hemophilia. You're a woman. You just bruise easily." We still have those horror stories today of a woman going in and her menstrual flow lasts for like three weeks, and she has a child and she almost bleeds to death. She got joint damage in her 20s or 30s. She's got all the hallmarks of having hemophilia, and even today, hematologists will tell women, "Well, hemophilia affects men. You're just a carrier."

As soon as a doctor says no, that starts to throw up roadblocks because that gives insurers an excuse to say, no, we're not going to cover expensive treatment therapies. So a big portion of our community's efforts now are about ensuring that our hemophilia sisters have the same quality and access to care that hemophilia brothers do. So we've got a bit of inequality even within our community, which is unfortunate.

Because I'm a community activist, I'm educated, I work in the community, I would feel confident handling my daughter's hemophilia. It doesn't bother me. Whether she does or she doesn't, I know we can have a full, thriving life with hemophilia.

We want to hear what you think about this article. Submit a letter to the editor or write to letters@theatlantic.com.

PR newswire.com
August 30, 2018

Bayer Receives FDA Approval for Jivi®, New Hemophilia A Treatment with Step-Wise Prophylaxis Dosing Regimen

Jivi's extended half-life allows for twice-weekly initial dosing and may be adjusted to every five days and further individually adjusted to less or more frequent dosing[1]

Whippany, NJ, -- **Bayer announced today that the U.S. Food and Drug Administration (FDA) has approved Jivi®** (BAY94-9027, antihemophilic factor [recombinant] PEGylated-aucl) for the routine prophylactic treatment of hemophilia A in previously treated adults and adolescents 12 years of age or older. The initial recommended prophylactic regimen for Jivi is twice weekly with the ability to dose every five days and further individually adjust to less or more frequent dosing based on bleeding episodes. The FDA also approved Jivi for on-demand treatment and the perioperative management of bleeding in the same population. This approval is based on results from the Phase 2/3 PROTECT VIII trial, which demonstrated bleed protection and safety of up to a median of 1.9 years (range of 0-2.6 years).[1] Jivi is the third FDA-approved hemophilia A treatment in Bayer's Hematology portfolio.

"As a physician who treats hemophilia A patients with a range of individualized needs, Jivi's approved dosing allows me to adjust frequency based on their bleed episodes to maintain protection from bleeds, which is a serious concern among patients," said Mark Reding, M.D., PROTECT VIII Lead Investigator and Associate Professor of Medicine at the University of Minnesota. "Jivi is a welcome option that addresses a growing patient need to integrate treatment with personal lifestyles."

Jivi works by replacing the reduced or missing factor VIII (FVIII) in adults and adolescents 12 years of age or older with hemophilia A. Through its site-specific PEGylation, Jivi has a half-life of 17.9 hours that delivers sustained levels in the blood.[1] Jivi is an important new treatment option in recombinant FVIII (rFVIII) replacement therapy. Recombinant factor VIII is the standard of care for hemophilia A and has proven efficacy and safety established over decades of clinical trials and real-world experience.

Treatment with Jivi was well tolerated in the majority of adult and adolescent patients in clinical trials. The most frequently reported adverse reactions in previously treated patients 12 years of age or older were headache, cough, nausea, and fever. A FVIII inhibitor (1.7 BU/mL) was reported in one previously treated adult subject. Repeat testing did not confirm the presence of a FVIII inhibitor.[1]

The FDA approval of Jivi is supported by results of the pivotal Phase 2/3 PROTECT VIII trial comprised of prophylactic dosing, on-demand treatment, and perioperative management in adults and adolescents 12 years of age or older with severe hemophilia A. One hundred and twenty-six patients completed the main study.[1]

"Today's approval builds on our 25-year partnership with the hemophilia community and underscores our commitment to developing new therapies that help meet the needs of patients living with this life-long disease," said Carsten Brunn, President of Bayer Pharmaceuticals, Americas Region. "Jivi's proven efficacy with its unique dosing regimen is an important benefit to patients that we look forward to bringing to the global community, as we pursue additional regulatory approvals for Jivi in other regions around the world."

Bayer has also submitted marketing authorization applications for BAY94-9027 for the treatment of hemophilia A in the European Union and Japan.

About Jivi (antihemophilic factor [recombinant] PEGylated-aucl)
Jivi is a recombinant factor VIII (rFVIII) replacement therapy, meaning it replaces the reduced or missing FVIII (a protein needed to form blood clots) in hemophilia A patients. Through its site- specific PEGylation, Jivi has a half-life of 17.9 hours that delivers sustained levels in the blood.[1]
Jivi is approved for the routine prophylactic treatment of hemophilia A in previously treated adults and adolescents 12 years of age or older. Jivi's initial recommended dosing regimen is twice weekly (30-40 IU/kg) with the ability to dose every five days (45-60 IU/kg) and further individually adjust to less or more frequent dosing based on bleeding episodes. The FDA also approved Jivi for on-demand treatment and the perioperative management of bleeding in the same population.[1]

About the PROTECT VIII Study
The PROTECT VIII study was a 36-week, Phase 2/3, international, open-label trial conducted in previously treated adults and adolescents 12 years of age or older with severe hemophilia A. Part A evaluated pharmacokinetics, efficacy and safety of Jivi for on-demand treatment of bleeds and for prophylactic therapy at different dosing regimens. An optional extension study was available to subjects who completed Part A to assess Jivi over at least 100 accumulated exposure days. Part B evaluated safety and efficacy of Jivi during major surgery.[1]

About Hemophilia A
Hemophilia has an estimated frequency of 1 in 5,000 male live births and affects approximately 400,000 people around the world, including an estimated 20,000 in the U.S. today.[2] It is a largely inherited disorder in which one of the proteins needed to form blood clots is missing or reduced. In hemophilia A, the most common type of hemophilia, blood clotting is impaired as a result of a lack or defect of coagulation factor VIII. Patients therefore repeatedly experience bleeds in muscles, joints or other tissues, which can result in chronic joint damage. External injuries, even if they seem trivial, can have serious consequences if not treated appropriately.
Hemophilia treatment has advanced considerably over the past decades, with life expectancy for people with hemophilia significantly increasing from about 11.4 years in 1920 to a potentially normal life span today.[3]

Bayer: Science for a Better Life
Bayer is a global enterprise with core competencies in the Life Science fields of health care and agriculture. Its products and services are designed to benefit people and improve their quality of life. At the same time, the Group aims to create value through innovation, growth and high

earning power. Bayer is committed to the principles of sustainable development and to its social and ethical responsibilities as a corporate citizen. In fiscal 2017, the Group employed around 99,800 people and had sales of EUR 35.0 billion. Capital expenditures amounted to EUR 2.4 billion, R&D expenses to EUR 4.5 billion. For more information, go to www.bayer.us.

Jivi Indications and Important Safety Information - Patients

INDICATIONS

- Jivi is an injectable medicine used to replace clotting factor (Factor VIII or antihemophilic factor) that is missing in people with hemophilia A.
- Jivi is used to treat and control bleeding in previously treated adults and adolescents (12 years of age and older) with hemophilia A. Your healthcare provider may also give you Jivi when you have surgery. Jivi can reduce the number of bleeding episodes in adults and adolescents with hemophilia A when used regularly (prophylaxis).
- Jivi is not for use in children below 12 years of age or in previously untreated patients.
- Jivi is not used to treat von Willebrand disease.

IMPORTANT SAFETY INFORMATION

- You should not use Jivi if you are allergic to rodents (like mice and hamsters) or to any ingredients in Jivi.
- Tell your healthcare provider about all of your medical conditions that you have or had.
- Tell your healthcare provider if you have been told that you have inhibitors to Factor VIII.
- Allergic reactions may occur with Jivi. Call your healthcare provider right away and stop treatment if you get tightness of the chest or throat, dizziness, decrease in blood pressure, or nausea.
- Allergic reactions to polyethylene glycol (PEG), a component of Jivi, are possible.
- Your body can also make antibodies, called "inhibitors," against Jivi, which may stop Jivi from working properly. Consult your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to Factor VIII.
- If your bleeding is not being controlled with your usual dose of Jivi, consult your doctor immediately. You may have developed Factor VIII inhibitors or antibodies to PEG and your doctor may carry out tests to confirm this.
- The common side effects of Jivi are headache, cough, nausea, and fever.
- These are not all the possible side effects with Jivi. Tell your healthcare provider about any side effect that bothers you or that does not go away.

For additional important risk and use information, please see the full Prescribing Information.

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

Our online press service is just a click away: www.bayer.us/en/newsroom
Follow us on Facebook: www.facebook.com/pharma.bayer

Follow us on Twitter: https://twitter.com/Bayerus

Find more information at www.bayerpharma.com.

Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

References:

[1] Jivi® [prescribing information]. Whippany, NJ: Bayer; 2018.

[2] Fast Facts (2015, July 15). Retrieved October 19, 2017, from: https://www.hemophilia.org/About-Us/Fast-Facts.

[3] Hemophilia and Aging (2014). Retrieved October 19, 2017, from: https://www.hemophilia.org/sites/default/files/document/files/Nurses-Guide-Chapter-17-Aging.pdf.

SOURCE Bayer
Related Links
http://www.bayer.us

Gene.com
August 29, 2018

Positive Phase III Results for Genentech's HEMLIBRA® (Emicizumab-kxwh) for Hemophilia A without Factor VIII Inhibitors Published in New England Journal of Medicine

– HEMLIBRA prophylaxis significantly reduced bleeds compared to no prophylaxis

– HEMLIBRA is the first medicine to demonstrate superior efficacy to prior factor VIII prophylaxis based on a statistically significant reduction in treated bleeds in an intra-patient comparison

– HEMLIBRA is currently under Priority Review by the FDA for people with hemophilia A without factor VIII inhibitors

(South San Francisco, CA) **– Genentech**, a member of the Roche Group, **announced today that pivotal data from the Phase III HAVEN 3 study**, which evaluated HEMLIBRA® (emicizumab-kxwh) prophylaxis administered every week or every two weeks in adults and adolescents aged 12 years or older with hemophilia A without factor VIII inhibitors, were published in the August 30, 2018, issue of the ***New England Journal of Medicine*** (*NEJM*).

"In the HAVEN 3 study, HEMLIBRA showed a significant and clinically meaningful reduction in bleeds in people with hemophilia A without factor VIII inhibitors, while offering multiple subcutaneous dosing options," said Dr. Johnny Mahlangu, Faculty of Health Sciences, University of the Witwatersrand and NHLS, Johannesburg, South Africa. "The publication of these results in the *New England Journal of Medicine* represents a major advance for hemophilia research and reinforces the potential of HEMLIBRA to change the standard of care for people with hemophilia A."

"Current prophylactic treatment options for people with hemophilia A can require frequent intravenous infusions, and despite treatment, many continue to have bleeds that can lead to long-term joint damage," said Sandra Horning, M.D., chief medical officer and head of Global Product Development. "Given the challenges many people face managing their hemophilia, we believe HEMLIBRA could make a meaningful difference, and we are working with health authorities to hopefully make this treatment available to people with hemophilia A without factor VIII inhibitors as soon as possible."

Data from the HAVEN 3 study showed that HEMLIBRA prophylaxis administered subcutaneously every week or every two weeks significantly reduced treated bleeds by 96 percent (rate ratio [RR]=0.04; $p<0.0001$) and 97 percent (RR=0.03; $p<0.0001$), respectively, compared to no prophylaxis. Results also showed that 55.6 percent (95 percent CI: 38.1; 72.1) of

people treated with HEMLIBRA every week and 60 percent (95 percent CI: 42.1; 76.1) of people treated with HEMLIBRA every two weeks experienced zero treated bleeds, compared to 0 percent (95 percent CI: 0.0; 18.5) of people treated with no prophylaxis. In an intra-patient comparison of people who previously received factor VIII prophylaxis in a prospective non-interventional study and switched to HEMLIBRA prophylaxis, HEMLIBRA demonstrated a statistically significant reduction of 68 percent (RR=0.32; $p<0.0001$) in treated bleeds, making it the first medicine to show superior efficacy to prior factor VIII prophylaxis treatment, the current standard of care. There were no unexpected or serious adverse events (AEs) related to HEMLIBRA in the HAVEN 3 study, and the most common AEs were consistent with previous studies. The most common AEs occurring in 5 percent or more of people were injection site reactions, joint pain (arthralgia), common cold symptoms (nasopharyngitis), headache, upper respiratory tract infection and influenza.

Earlier this year, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy Designation and Priority Review to HEMLIBRA for people with hemophilia A without factor VIII inhibitors based on data from the HAVEN 3 study. The FDA is expected to make a decision on approval by October 4, 2018. Breakthrough Therapy Designation is designed to expedite the development and review of medicines intended to treat a serious condition with preliminary evidence that indicates they may demonstrate substantial improvement over existing therapies. Priority Review designation is granted to medicines that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a serious disease. Submissions to other regulatory authorities around the world are ongoing.

About HAVEN 3 (NCT02847637)
HAVEN 3 is a randomized, multicenter, open-label, Phase III study evaluating the efficacy, safety and pharmacokinetics of HEMLIBRA prophylaxis versus no prophylaxis (episodic/on-demand factor VIII treatment) in people with hemophilia A without factor VIII inhibitors. The study included 152 patients with hemophilia A (12 years of age or older) who were previously treated with factor VIII therapy either on-demand or for prophylaxis. Patients previously treated with on-demand factor VIII were randomized in a 2:2:1 fashion to receive subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 1.5 mg/kg/wk for at least 24 weeks (Arm A), subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 3 mg/kg/2wks (Arm B) for at least 24 weeks or no prophylaxis (Arm C) for at least 24 weeks. Patients previously treated with factor VIII prophylaxis received subcutaneous HEMLIBRA prophylaxis at 3 mg/kg/wk for 4 weeks, followed by 1.5 mg/kg/wk until the end of study (Arm D). Episodic treatment of breakthrough bleeds with factor VIII therapy was allowed per protocol.

The Phase III HAVEN 3 study in people with hemophilia A without factor VIII inhibitors met its primary endpoint and key secondary endpoints. Data from the study showed:

- HEMLIBRA prophylaxis every week or every two weeks resulted in a 96 percent (RR=0.04; p<0.0001) and 97 percent (RR=0.03; p<0.0001) reduction in treated bleeds, respectively, compared to no prophylaxis.
- 55.6 percent (95 percent CI: 38.1, 72.1) of people treated with HEMLIBRA every week and 60 percent (95 percent CI: 42.1, 76.1) of people treated with HEMLIBRA every two weeks experienced zero treated bleeds, compared to 0 percent (95 percent CI: 0.0; 18.5) of people treated with no prophylaxis.
- 91.7 percent (95 percent CI: 77.5, 98.2) of people treated with HEMLIBRA prophylaxis every week and 94.3 percent (95 percent CI: 80.8, 99.3) of people treated with HEMLIBRA prophylaxis every two weeks experienced three or fewer treated bleeds, compared to 5.6 percent (95 percent CI: 0.1, 27.3) of people treated with no prophylaxis.
- HEMLIBRA prophylaxis every week or every two weeks resulted in a 95 percent (RR=0.05; p<0.0001) and 95 percent (RR=0.05; p<0.0001) reduction in treated target-joint bleeds, respectively, compared to no prophylaxis.
- HEMLIBRA prophylaxis every week or every two weeks resulted in a 95 percent (RR=0.05; p<0.0001) and 94 percent (RR=0.06; p<0.0001) reduction in all bleeds, respectively, compared to no prophylaxis.
- HEMLIBRA prophylaxis every week demonstrated a statistically significant reduction of 68 percent (RR=0.32; p<0.0001) in treated bleeds compared to prior factor VIII prophylaxis based on an intra-patient comparison of people who were previously enrolled in a prospective non-interventional study.
- There were no unexpected or serious AEs related to HEMLIBRA, and the most common AEs were consistent with previous studies. No thrombotic events or cases of thrombotic microangiopathy were observed. The most common AEs occurring in 5 percent or more of people were injection site reactions, joint pain (arthralgia), common cold symptoms (nasopharyngitis), headache, upper respiratory tract infection and influenza.

About HEMLIBRA

HEMLIBRA is a bispecific factor IXa- and factor X-directed antibody. It is designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood clotting process for hemophilia A patients. HEMLIBRA is a prophylactic (preventative) treatment that can be administered by an injection of a ready-to-use solution under the skin (subcutaneously) once weekly. HEMLIBRA was created by Chugai Pharmaceutical Co., Ltd. and is being co-developed globally by Chugai, Roche and Genentech.

HEMLIBRA U.S. Indication

HEMLIBRA is a prescription medicine used for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A with factor VIII inhibitors.

Important Safety Information

What is the most important information to know about HEMLIBRA?

HEMLIBRA increases the potential for blood to clot. Discontinue prophylactic use of bypassing agents the day before starting HEMLIBRA prophylaxis. Carefully follow the healthcare provider's instructions regarding when to use an on-demand bypassing agent, and the dose and schedule one should use. Cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of activated prothrombin complex concentrate (aPCC) was administered for 24 hours or more to patients receiving HEMLIBRA prophylaxis.

HEMLIBRA may cause the following serious side effects when used with aPCC (FEIBA®), including:

- **Thrombotic microangiopathy (TMA).** This is a condition involving blood clots and injury to small blood vessels that may cause harm to one's kidneys, brain, and other organs. Patients should get medical help right away if they have any of the following signs or symptoms during or after treatment with HEMLIBRA:
    - confusion
    - weakness
    - swelling of arms and legs
    - yellowing of skin and eyes
    - stomach (abdomen) or back pain
    - nausea or vomiting
    - feeling sick
    - decreased urination

- **Blood clots (thrombotic events).** Blood clots may form in blood vessels in one's arm, leg, lung or head. Patients should get medical help right away if they have any of these signs or symptoms of blood clots during or after treatment with HEMLIBRA:
    - swelling in arms or legs
    - pain or redness in the arms or legs
    - shortness of breath
    - chest pain or tightness
    - fast heart rate
    - cough up blood
    - feel faint
    - headache
    - numbness in the face
    - eye pain or swelling
    - trouble seeing

If aPCC (FEIBA®) is needed, patients should talk to their healthcare provider in case they feel they need more than 100 U/kg of aPCC (FEIBA®) total.

Before using HEMLIBRA, patients should tell their healthcare provider about all of their medical conditions, including if they:

- are pregnant or plan to become pregnant. It is not known if HEMLIBRA may harm an unborn baby. Females who are able to become pregnant should use birth control (contraception) during treatment with HEMLIBRA.
- are breastfeeding or plan to breastfeed. It is not known if HEMLIBRA passes into breast milk.

What should patients know about lab monitoring?
HEMLIBRA may interfere with laboratory tests that measure how well blood is clotting and may cause a false reading. Patients should talk to their healthcare provider about how this may affect their care.

The most common side effects of HEMLIBRA include: redness, tenderness, warmth, or itching at the site of injection; headache; and joint pain.

These are not all of the possible side effects of HEMLIBRA. Patients should call their doctor for medical advice about side effects.

Side effects may be reported to the FDA at (800) FDA-1088 or http://www.fda.gov/medwatch. Side effects may also be reported to Genentech at (888) 835-2555.

Please see the HEMLIBRA full **Prescribing Information** and the **Medication Guide**, including **Serious Side Effects**, for more important safety information.

About Hemophilia A
Hemophilia A is an inherited, serious disorder in which a person's blood does not clot properly, leading to uncontrolled and often spontaneous bleeding. Hemophilia affects around 20,000 people in the United States, with hemophilia A being the most common form and approximately 50-60 percent of people living with a severe form of the disorder.

People with hemophilia A either lack or do not have enough of a clotting protein called factor VIII. In a healthy person, when a bleed occurs, factor VIII brings together the clotting factors IXa and X, which is a critical step in the formation of a blood clot to help stop bleeding. Depending on the severity of their disorder, people with hemophilia A can bleed frequently, especially into their joints or muscles. These bleeds can present a significant health concern as they often cause pain and can lead to chronic swelling, deformity, reduced mobility and long-term joint damage.

A serious complication of treatment is the development of inhibitors to factor VIII replacement therapies. Inhibitors are antibodies developed by the body's immune system that bind to and block the efficacy of replacement factor VIII, making it difficult, if not impossible, to obtain a level of factor VIII sufficient to control bleeding.

About Genentech in Hemophilia
In 1984, Genentech scientists were the first to clone recombinant factor VIII in response to the contaminated hemophilia blood supply crisis of the early 1980s. For more than 20 years, Genentech has been developing medicines to bring innovative treatment options to people with diseases of the blood

within oncology, and in hemophilia A. Genentech is committed to improving treatment and care in the hemophilia community by delivering meaningful science and clinical expertise. For more information visit http://www.gene.com/hemophilia.

About Genentech

Founded more than 40 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes medicines to treat patients with serious and life-threatening medical conditions. The company, a member of the Roche Group, has headquarters in South San Francisco, California. For additional information about the company, please visit http://www.gene.com.

##