THE 11th WFH GLOBAL FORUM

on Research and Treatment Products for Bleeding Disorders

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PROCEEDINGS

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Proceedings of the 11th WFH Global Forum on Research and Treatment Products for Bleeding Disorders

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EXECUTIVE SUMMARY

The 11th WFH Global Forum on Research and Treatment Products for Bleeding Disorders held in Montreal, November 13-14, 2019, focused on current topics and challenges of foremost importance in safety, supply, and availability of therapies for hemophilia, von Willebrand disease, and other inherited bleeding disorders. This year's meeting assembled nearly 200 participants from around the world comprising key stakeholders: patients, healthcare providers, scientists and researchers, regulatory officials, and industry representatives. Sessions explored a wide range of topics: blood and plasma safety, efficacy and safety of extended half-life (EHL) products and non-factor products, point-of-care diagnosis, access to affordable treatment products and humanitarian aid, new and novel hemophilia therapies, gene and cell therapies, data collection, von Willebrand disease (VWD), and women with bleeding disorders. The ultimate goal is to fulfill the unmet needs in diagnosis, treatment, and access to care.

Blood safety and plasma safety

In this era of new technologies and new types of treatment such as EHL clotting factor concentrates (CFCs) and non-factor replacement therapies, and development of hemophilia gene therapies, it is important to ensure that existing safe and effective treatment options not be left behind. This session addressed the continuing importance of fresh blood components and plasma-derived CFCs with standard half-life (SHL) to the global bleeding disorders community and the need for strategies to ensure continuing access and availability.

Presentations described the impacts and implications of key developments in the past decade, particularly the development of solvent detergent viral-inactivated cryoprecipitate products, efforts to introduce low-dose prophylaxis, and the phenomenal expansion of WFH Humanitarian Aid Program. The session also included an overview of World Health Organization (WHO) initiatives to advance the quality and availability of blood components. The WHO identified blood components as essential medicines in 2013, and in 2017 published Guidelines on Management of Blood and Blood Components as Essential Medicines. Efforts to reduce the gap in availability of treatment products for bleeding disorders in low- and middle-income countries include initiatives to expand the supply of recovered plasma suitable for fractionation, and recent advocacy for local production of pathogen-reduced cryoprecipitate in settings where CFCs are unavailable, unaffordable or in limited supply.

Extended half-life products

Extended half-life CFCs provide the ability to optimize and tailor treatment and achieve higher factor trough levels than standard half-life CFCs. Higher trough levels, in addition to better protection against bleeds in general, may be important to better prevent or minimize subclinical bleeding (i.e., microbleeds) and spontaneous bleeding. Data have shown large inter-patient variability in clearance across EHL CFCs. This has implications for the debate surrounding what defines an EHL product. EHL CFCs provide the flexibility to tailor dosing to target the same level of protection as with SHL CFCs by maintaining the same target dose level while reducing the frequency of treatment; or by aiming for a higher level of protection by targeting a higher dose level while maintaining the same frequency of treatment.

EHL CFCs based on polyethylene glycol (PEG) have been approved and are use in some countries. PEGylated CFCs have been well tolerated in both clinical and non-clinical studies. Histological findings of PEG accumulation and vacuolation is a possible concern for lifelong chronically administered PEGylated drugs; however, the doses of PEGylated CFCs are generally significantly below doses at which this is seen. Long-term consequences and clinical hallmarks of PEG accumulation are not known; more safety data, particularly in the pediatric population, are needed.

Non-factor products
Non-replacement products can be used in patients with or without inhibitors, have no troughs or peaks, and can be administered subcutaneously. Furthermore, they have demonstrated a reduction in annualized bleeding rates. Two important questions are how to monitor target protein in clinical laboratories and how to their equivalence relative to factor replacement therapies. Dose response is also an area that requires more investigation. Work is ongoing in developing assays specific to the various products. Adverse events rates appear similar to other available products but it is too early to be certain. It is important to note that immunogenicity in the early phases of clinical development is not always predictive of immunogenicity in real-world clinical use. Early results suggest that emicizumab prophylaxis is effective and safe in very young children, but caution is advised when interpreting global assay results, and correlation with the clinical setting is essential. The introduction of EHL products and emicizumab to the product mix makes it difficult to measure hemophilia care using a single metric and challenging to understand usage levels and cost.

Point-of-care diagnosis
Increasing diagnosis and identification of people with hemophilia and other inherited bleeding disorders are key aspects of the WFH's overall mission of treatment for all. To confirm diagnosis, laboratory testing is required to identify and confirm the coagulation defect. Ideally, standard coagulation tests should be performed in a central laboratory, but this is sometimes difficult in real life. Point-of-care devices could offer new and more convenient modalities for diagnosis and monitoring of hemophilia and other bleeding disorders. Several projects are underway to develop point-of-care devices that can be used in clinic for testing and diagnosis quickly and affordably, and by patients for self-monitoring of treatment.

Ensuring access to affordable treatment products and humanitarian aid
This session looked the evolution of the hemophilia treatment market and the impacts of new innovations on access over the last three decades, as well as WFH programs to ensure access to affordable treatment products and humanitarian aid in countries with limited resources. The introduction of recombinant factor products in the 1990s increased the global supply of factor VIII (FVIII) and factor IX (FIX) concentrates far beyond what could be manufactured from plasma. Recently introduced recombinant EHL products have further increased the CFC supply. Furthermore, non-factor products offer further cost reductions and are expected to increase the volume of therapies available to patients. Gene therapy also has the potential to radically change hemophilia treatment, and to make nearly universal access to hemophilia treatment possible in the long run if hurdles are overcome.

The WFH Humanitarian Aid Program was started in 1996 with the aim of improving the lack of global access to care and treatment for people with inherited bleeding disorders in developing countries through the distribution of surplus CFCs donated by pharmaceutical companies. A three-year expansion of the program from 2015 to 2018 led to a substantial increase in the volume of humanitarian aid donations, enabling healthcare professionals to fully treat patients with bleeding disorders according to international standards and the WFH treatment guidelines. In addition to acute bleeding episodes and life-threatening surgeries, healthcare professionals are now also able to perform corrective surgeries and procedures; provide prophylactic treatment, including low-dose prophylaxis for children under 4 years of age; and provide immune tolerance induction therapy for hemophilia patients with inhibitors. The program's reach increased exponentially, from 3,767 people with hemophilia receiving emergency life-threatening treatment in 2015 to 18,458 patients receiving treatment in 2018 for acute bleeds, surgeries, and prophylaxis.

The Global Alliance for Progress (GAP) was launched in 2003 to close the gaps in treatment and care around the world, and between the estimated and identified number of people with bleeding disorders, the number of people born with hemophilia and those who reach adulthood, and the need versus the availability of treatment products. The key objectives are to foster partnerships and work with patient organizations, healthcare providers, and government to develop sustainable national care programs in developing countries. The GAP program has involved over 30 countries to date, with close to 20 active partnerships in 2019.

Strategies to improve access include an open, fair, and transparent procurement system involving hemophilia clinicians and expert patient representatives in the process, removal of unnecessary costs or steps (e.g., distributor margins, handling fees), recognition of disparities in taxation of products, and economies of scale (e.g., multi-year commitments and larger purchases for the entire country).

New and novel hemophilia therapies

Presentations in this session described several novel hemophilia therapies in development: anti-TFPI (tissue factor pathway inhibitor) antibodies; gene therapies for hemophilia A and B; *ex vivo* gene-modified allogeneic human cells to correct bleeding disorders; and *in vivo* genome editing for hemophilia. In addition, reports were presented on the use of COX-2 inhibitors in hemophilia, and safety of recombinant factor VIII-Fc in children. The use of select COX-2 inhibitors as pain medication for hemophilic arthropathy expands the treatment options which would otherwise be limited to acetaminophen and opioids, and provides important benefits including better pain management and decreased risk of gastrointestinal bleeding (GI). However, it is important to evaluate and monitor existing conditions (e.g., GI bleeding, cardiovascular or renal disease). Clinical studies showed that rFVIIIFc is generally well-tolerated by pediatric patients; there were no cases of inhibitors during clinical studies in previously treated patients and adverse events were consistent with those expected in the hemophilia population. The safety profile of rFVIIIFc is supported by more than 5 years of real-world post-marketing experience.

Data collection

The session on data collection described the 20-year history of the WFH Annual Global Survey, and updated estimations and estimates of hemophilia prevalence. The prevalence of hemophilia is now estimated to be between 800,000 and just over 1 million people with hemophilia worldwide, approximately 3 times higher than previously estimated. Also reviewed were the European Medicines Agency's move from post-marketing surveillance to a registry system for long-term follow-up, and development and implementation of the WFH World Bleeding Disorders Registry and the World Hemophilia Gene Therapy Registry.

Gene and cell therapy

Gene therapies for hemophilia are very far advanced in clinical development. However, high cost and complexity of development and manufacture are part of the ongoing challenges in this field. Most gene therapies being developed rely on adeno-associated virus (AAV) vectors for gene transfer. However, there are challenges related to high vector doses, immune response, and limited patient population. Furthermore, the long-term efficacy and safety are unknown and will require close post-marketing surveillance and long-term follow-up. High AAV antibody seroprevalence, high inter-patient variability in response, and unknown causes of transient transaminase elevations also require further investigation. The regulatory pathway for gene therapy products was described.

Recent development of gene-editing technologies and therapies for hemophilia have shown promising results in early clinical development, and may potentially lead to a cure for hemophilia. Non-viral vectors have been developed to deliver small molecule drugs and antisense

oligonucleotides but require development and optimization to deliver large molecules such as mRNA/gRNA, RNP, or ssDNA. Investigation of feasible vector, dose, and safety and efficacy is ongoing.

Von Willebrand disease and women and bleeding disorders

The final session presented an overview of treatment options for preventing or treating bleeding in patients with von Willebrand disease, which comprise antifibrinolytic therapy, desmopressin, and factor concentrates. Several studies on prophylaxis in VWD have shown significantly decreased bleeding in patients on prophylaxis, particularly less epistaxis and GI bleeding. There remain gaps in data on optimal treatment of VWD with factor replacement therapy, particularly for management of heavy menstrual bleeding, pregnancy, and post-partum hemorrhage; and in surgical procedures, particularly for tonsillectomy and colon polypectomy. Development of updated guidelines for the diagnosis and management of VWD is underway by the American Society of Hematology (ASH) in collaboration the International Society on Thrombosis and Haemostasis (ISTH), U.S. National Hemophilia Foundation (NHF), and WFH, to be published in 2020.

The session also addressed current and common understanding of carriers of hemophilia, issues surrounding nomenclature and definitions, and challenges and needs in the management of care. It has been recognized that about one-third of hemophilia carriers have low factor levels below 40% and experience abnormal bleeding, most frequently heavy menstrual bleeding, and postpartum hemorrhage. There is an urgent need to gather data through patient registries. Increased awareness among treaters and patients is still needed.

WELCOME REMARKS

Alain Weill, President of the World Federation of Hemophilia (WFH), welcomed a record 199 participants to the 11th WFH Global Forum on Research and Treatment Products for Bleeding Disorders, held in Montreal, November 13-14, 2019. He anticipated the exchange of high-level science and dialogue, and highlighted two key challenges: addressing the gaps between expected and observed hemophilia prevalence rates in countries across the world, and increasing access to treatment globally.

A newly published study on hemophilia prevalence, incidence, and prevalence at birth, along with data from the WFH Annual Global Survey, show that the percentage of people with hemophilia identified, relative to the expected prevalence, varies widely across countries and regions. About 74% of people with hemophilia have been identified in Europe in comparison to 7% identified in Africa. About 25% of people with hemophilia worldwide have been identified. Factor consumption also varies significantly by geographic area, and by gross national income. High-income countries, which represent 15% of the world population, consume 64% of the total factor VIII supply globally; high and upper middle-income countries combined, which together represent 51% of the world population, consume about 94% of the global FVIII supply. Finding solutions for these challenges should be kept in mind throughout the Global Forum, Mr. Weill said.

Dr. Glenn Pierce, WFH Vice President, Medical, noted that the Global Forum has evolved over 20 years, broadening its focus from blood safety and supply to encompass a wider range of topics related to current and ongoing issues in the hemophilia and bleeding disorders community. It is a unique forum that combines medicine and technology with policy and advocacy. The focus this year was where global treatment is headed, how to get there, and what data are required towards achieving the goals.

Throughout the forum, the audience was polled to gauge their perspectives on current issues, including changes in perspectives over the course of the sessions. In the first poll, 65% of respondents considered the biggest threat for patients today to be supply and access to treatment products; while 24% considered inhibitors to be the biggest threat. and 64% of respondents saw price as the biggest threat to supply, while 15% considered regulatory issues to be the biggest supply threat. In addition, 30% of respondents felt that gene therapy would be commercially available to patients in 1 year, while 29% felt it would take 3 years, and 41% estimated availability in 5 years. Poll questions and results can be found at the end of the proceedings. He thanked the 2019 sponsors for funding support: Bayer, Roche, Spark, and uniQure.

BLOOD SAFETY AND PLASMA SAFETY

CHAIR: MARK W. SKINNER, INSTITUTE FOR POLICY ADVANCEMENT, WASHINGTON, DC, USA

One of the hallmarks of the WFH Global Forum is the exchange of the latest in hemophilia research, treatment, and clinical practice to support understanding of policy issues and the importance of global development of hemophilia care. In this era of new treatments and new technologies, it is important to ensure that the existing effective treatment options not be left behind, Mr. Mark Skinner said.

Pathogen safety in the bleeding disorders global community

MARK W. SKINNER, INSTITUTE FOR POLICY ADVANCEMENT, WASHINGTON, DC, USA

Mr. Skinner set the stage for a discussion of the use of labile blood components around the world. Over the past 10 years, there have been several key developments related to the pathogen safety and use of labile blood components for bleeding disorders treatment: the availability of a new technique for processing small plasma volumes to produce solvent-detergent viral-inactivated cryoprecipitate products, efforts to introduce low-dose prophylaxis, and the expansion of WFH Humanitarian Aid Program.

The WFH strongly recommends the use of viral inactivated plasma-derived or recombinant clotting factor concentrates for the treatment of hemophilia and other inherited bleeding disorders over cryoprecipitate or fresh frozen plasma (FFP), as CFCs have superior safety and efficacy. The WFH's position is that the use of cryoprecipitate and FFP can only be justified in situations where CFCs are not available, and in the transition to CFCs where resource constraints exist. Others in the global hemophilia community advocate sustained production of virally inactivated cryoprecipitate integrated into routine operations of blood establishments within a local framework of capacity building of the blood system to alleviate shortage or unaffordability of CFCs products for treatment of hemophilia A. Current debate surrounds whether these two positions can be reconciled.

Data from the WFH Annual Global Survey for 2018 show that, particularly in lower-income and lower middle-income countries, use of cryoprecipitate and FFP is still common. Fresh blood components remain important treatment for hemophilia in many parts of the world and should not be forgotten as new treatment advances, due to new technologies that provide substantially enhanced efficacy, continue to revolutionize hemophilia care, Mr. Skinner said. However, he noted that increased product donations and multi-year commitments to the WFH Humanitarian Program now make it possible for those most in need to have continued access to CFCs for emergency situations, acute bleeds, corrective surgeries, and to initiate prophylaxis for young children. This evolution in greater availability of virally inactivated products and the evidence showing the superiority of low-dose prophylaxis over episodic treatment are changing the thinking about treatment options and avenues for advancing hemophilia care in many countries.

Emerging risks and pathogen safety

MICHAEL P. BUSCH, MD, PHD, VITALANT RESEARCH INSTITUTE; UNIVERSITY OF CALIFORNIA, SAN FRANCISCO, USA

Dr. Michael Busch provided an overview of transfusion-transmitted infections (TTIs) and risk reduction over the past 50 years. The initial approaches to reduce TTI risks were predominantly based on screening until advances in viral discovery and the development of diagnostic testing in the late 1970s. Over time, improvements to these measures and increasingly sensitive laboratory methods including immunoassays and nucleic acid–based tests have reduced infection risk rates significantly from peaks of 10% hepatitis C (HCV) and hepatitis B (HBV) transmission and up to 1% HIV transmission to the 1 in 1 million range.

A key development has been the evolution of serologic testing. The vast majority of HIV infections are interdicted by HIV Ag/Ab Combo assay screening. The scientific community should consider phasing out some serological tests given that current inactivation steps are highly robust and as a cost-saving measure, Dr. Busch said. He reviewed global response and testing for various emerging bloodborne and transfusion transmissible viruses such as Zika virus, West Nile virus, and others. Some emerging viruses have proven to not be a threat, while others have been found to cause serious

disease and present legitimate risks to the blood supply. All emerging viruses of concern need to be investigated to generate evidence on the presence or absence of risk to inform policy decisions.

Recently, blood screening concerns have been raised regarding blood donations from individuals on anti-retroviral therapy (ART) and pre-exposure prophylaxis (PrEP). Current testing with typical HIV antibody and mini-pool NAT blood donor screening may not be able to detect HIV infections in donors on ART/PrEP. The Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P) Supplemental project is studying the impact of ART and PrEP using FDA-licensed and pre-licensure versions of HIV donor screening NAT and serological tests. Key aims are to document enhanced detection of HIV-infected donors and high-risk individuals on PrEP by NAT viral (NAT/VL) assays in whole blood relative to plasma; and demonstrate that sensitive multiplexed HIV antigen assays can detect humoral immune responses not detected by commercial assays in individuals on ART and PrEP.

WHO efforts to advance quality and availability of blood components

JAY EPSTEIN, MD, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Dr. Jay Epstein gave an overview of World Health Organization (WHO) blood donation and blood safety initiatives over the past two decades. In 2010, it was estimated that over 9 million litres of recovered plasma that could be obtained from whole blood is not being produced for lack of component separation, or was being discarded for lack of clinical need and unsuitability for fractionation. The WHO has worked to advance the quality and availability of blood components through strengthening of blood systems and blood regulation, particularly in low- and middle-income countries, and resolutions adopted by the World Health Assembly (WHA), its decision-making body.

- In 2005, WHA Resolution 58.13 set out a goal to assure access to safe blood for all patients requiring transfusion and established World Blood Donor Day.
- In 2010, WHA Resolution 63.12 asserted the importance of stringent regulatory control and national blood regulations to ensure that the quality and safety of blood products across the entire transfusion chain meet internationally recognized standards.
- In 2012, the WHO Achilles Project was established to expand the availability of recovered plasma for fractionation through in-country implementation of Quality Systems and Good Manufacturing Practices in blood component preparation meeting international standards. The WHO also published Guidelines on Management of Blood and Blood Components as Essential Medicines, and Assessment Criteria for National Blood Regulatory Systems.
- In 2013, blood components (whole blood, red blood cells, platelets, and fresh frozen plasma) were added to the WHO's Model List of Essential Medicines.
- In 2014, WHA Resolution 67.20 recognized the importance of regulatory system strengthening to increase access to safe, effective, and quality medical products, and attain better public health outcomes.
- In 2017, the WHO introduced its Global Benchmarking Tool for the assessment of regulatory systems for medical products. Revisions were made in 2018 incorporating criteria for assessing regulation of vaccines and pharmaceuticals, and in 2019 incorporating assessment criteria for national blood regulatory systems and blood product regulation.

Dr. Epstein noted that the International Society of Blood Transfusion (ISBT) Working Party on Global Blood Safety issued recommendations in 2018 on increasing availability of recovered plasma for

fractionation, which advocated local production of virus-inactivated cryoprecipitate in resource-limited settings where commercial CFCs are unavailable, unaffordable, or in limited supply. The WHO Blood Regulators Network likewise advocates use of pathogen-reduced cryoprecipitate in resource-limited settings until CFCs are available and affordable, subject to a careful assessment of risks and benefits and an organized nationally regulated blood system operating under good practices for the preparation of medicinal products in healthcare establishments.

Panel discussion

Pathogen-reduced cryoprecipitate is an important option in resource-limited settings that fulfills the criteria for sustainable adequate treatment because it fits within existing structures and budgets, and covers clinical needs not only for hemophilia A and von Willebrand disease but other conditions as well, said Dr. Jean Claude Faber (Luxembourg). There currently is only one validated technology available to treat cryoprecipitate whereas there are validated technologies for treating plasma such as the Intercept and Mirasol systems. In collaboration with industry, the WFH could work to facilitate the application of these technologies or further the development of new technologies for pathogen reduction of cryoprecipitate in developing countries. Dr. Glenn Pierce, WFH VP Medical, replied that cryoprecipitate is an important interim measure where CFCs are not available, whereas the Humanitarian Aid Program takes a different approach that is focused on providing large quantities of factor products to at least some of the countries in need. Approximately 19,000 patients are treated with WFH humanitarian aid products on a yearly basis, and numbers will increase with new industry donors having joined the program.

Cryoprecipitate and factor concentrates are not necessarily incongruent treatment options—developing countries can be in transition for years or decades, therefore the goal is not just about blood safety but also about raising the efficacy of care for patients, said Dr. Steven Pipe (USA). Cryoprecipitate is insufficient to avoid joint damage so it should not be the endpoint or aspiration even in lower- and middle-income countries, but meanwhile there must be sustainable options to support countries through the transition years.

EXTENDED HALF-LIFE PRODUCTS

CHAIR: BRIAN O'MAHONY, IRISH HAEMOPHILIA SOCIETY, DUBLIN, IRELAND

Mr. Brian O'Mahony opened the session on extended half-life products with an audience poll on the value of defining an extended half-life product. According to the survey, 43% of participants felt that definition of "extended half-life" will address current confusion as to which products are standard half-life and which are extended half-life; 30% felt it will help patients with choice of products to use; and 14% felt it will help payers make reimbursement decisions. Survey results shifted significantly when the audience poll was repeated at the end of the session; 65%, 23%, and 7% respectively.

Pharmacokinetics to manage patients

ALFONSO IORIO, MD, CONGENITAL BLEEDING DISORDERS CLINIC, MCMASTER UNIVERSITY MEDICAL CENTRE, HAMILTON, CANADA

Until recent years, pharmacokinetic (PK) data were only used to establish drug efficacy in clinical drug development and the drug registration process. Extended half-life products have introduced a new and interesting dimension the association between plasma factor activity levels and bleeding rate or risk, and offer the opportunity to target personalized and higher levels of protection that are more difficult to achieve with standard half-life products, Dr. Alfonso Iorio said.

The use of population PK data together with individual patient data in the management of hemophilia makes it possible to predict individual PK parameters using fewer samples than the traditional approach, which then can be used to derive individual PK profiles. There is educational value in being able to show each patient their own PK profile. For example, a comparison of a patient's PK profile on SHL vs. EHL factor would show the levels of protection that can be achieved depending on parameters such as infusion interval, trough level, and time above threshold (TAT). Individual PK data can be used to determine precisely when it is safe to engage in certain types of sports and activities. This individual data can be used to develop a tailored treatment regimen, which can be done in clinic by the clinician together with the patient.

Dr. Iorio described the Web-Accessible Population Pharmacokinetic Service – Hemophilia (WAPPS – Hemo) repository used by a global network of hemophilia treatment centres; and the WAPPS app, which is used by patients to record personal treatment data. WAPPS – Hemo is a database of patient PK data for all existing factor concentrates, which are also used for population PK modelling, individualized PK estimations, and PK-tailored dosing. Patient PK data collected by WAPPS show significant interpatient variability, with a three-fold range in PK parameters for any concentrate. This has implications for the debate surrounding what defines an EHL product, and should also be kept in mind when considering the appropriate treatment regimen for an individual patient. Individualized treatment and PK-tailored prophylaxis offer significant potential for societal and individual savings, and reduction of wastage. Population PK data have shown the feasibility and benefits of low-dose prophylaxis. Data from a 2019 Chinese study show that factor clearance plays a role in half-life; and that while higher doses reach higher levels, factor levels drop to around 2% within about the same amount of time as lower doses.

There are differences between hemophilia A and B. For instance, in hemophilia A, factor VIII levels change over time and in response to exercise; in hemophilia B, the association between plasma level and effect is more complex than previously thought. Nonetheless, for both hemophilia A and B, integration of population PK with individual patient data allows the clinician to modulate the intensity of treatment in response to the required level of protection. Dr. Iorio concluded by noting that his group is in conversation with the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) about using WAPPS–Hemo data to redefine labelling information using data collected from many more patients than currently.

A pragmatic definition of EHL rFVIII

JOHNNY MAHLANGU, MD, UNIVERSITY OF THE WITWATERSRAND; CHARLOTTE MAXEKE JOHANNESBURG HOSPITAL, JOHANNESBURG, SOUTH AFRICA

Extended half-life products provide physicians and patients with a lot of flexibility to tailor and optimize treatment regimens according to the patient's particular goals or circumstances, Dr. Johnny Mahlangu said. EHL dosing can target the equivalent factor levels as achieved with standard half-life factor but with fewer infusions per week without compromising efficacy. Or, EHL dosing can target higher factor levels and higher levels of protection than achieved with SHL CFCs through higher dosage and frequency. With SHL CFCs, the common understanding is that peak factor levels play a role in preventing bleeds due to trauma or physical activity. With EHL CFCs, the ability to optimize the factor-level area under the curve (AUC) and achieve higher factor trough levels, in addition to preventing bleeds in general, may be important to better prevent or minimize subclinical bleeding (i.e., microbleeds) and spontaneous bleeding.

Pharmacokinetic parameters such as factor half-life, factor clearance, and AUC are critical factors in achieving and maintaining target factor levels. However, factor activity levels after infusion differ according to an individual patient's pharmacokinetics. A clear definition of EHL factor is needed, particularly for payers to understand the distinct properties and benefits. A pragmatic definition of EHL FVIII has been proposed by an international group of experts based on a systematic literature search and critical analysis of the published data.

To be defined as an EHL FVIII, all the following criteria should be met:

- designed with technology to extend biological half-life (e.g. polyethylene glycol, PEGylation);
- fulfills criteria for "biodifference" compared with standard FVIII for the majority of patients (in contrast to bioequivalence);
- half-life extension ratio of 1.3 or higher and increased AUC.

The FDA/EMA regulatory definition of non-bioequivalence could be used as valid criteria to help define an EHL factor product (that the 90% confidence interval of the AUC ratio is beyond the regulatory-defined bioequivalence window of 80–125%). To be viable and useful, these definitions should correlate and be true to the advantages, improved patient outcomes, and better treatment management achievable with EHL products, Dr. Mahlangu said.

Are EHLs less immunogenic and can they promote tolerance induction?

STEVEN W. PIPE, MD, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN, USA

Immune tolerance induction (ITI) is a substantial burden for both hemophilia patients and caregivers, with estimated time to tolerization ranging from 18.5 to 30.2 months, said Dr. Steven Pipe. This has significant financial implications, including on the cost of ITI treatment regardless of type of standard half-life factor used ($50,000-$75,000 per month) and additional high costs associated with continued use of bypassing agents.

A number of recent case reports show the tolerogenic potential of recombinant FVIII-Fc fusion protein (rFVIIIFc) in ITI; four children with severe hemophilia A and high-responding inhibitors were successfully treated using different doses of rFVIIIFc ITI (ranging from 50 to 200 IU/kg per dose) and appeared to achieve recovery at a faster rate than is seen with SHL factors.

Dr. Pipe highlighted assumptions based on a pragmatic definition of EHLs as applied to tolerogenic potential. Extended half-life, increased AUC of exposure to the immune system, and mechanism of action are likely important to tolerogenic potential. While EHL products are similar in their half-life extending properties, they each have very different mechanisms of action (i.e., Fc fusion, albumin fusion, PEGylation) and are not alike in terms of tolerogenic potential.

Dr. Pipe reviewed findings from a retrospective analysis of outcomes of ITI with rFVIIIFc in patients with severe hemophilia A and high-titer inhibitors.

- In this patient population with high-risk features for ITI failure, rFVIIIFc demonstrated a rapid decrease in Bethesda titer and rapid tolerization in first-time ITI patients.
- For rescue ITI, rFVIIIFc showed therapeutic benefit in patients who have previously failed ITI with other products and rapid tolerization in many rescue ITI patients.
- A trend toward rapid decrease in Bethesda titer was observed with higher rFVIIIFc dosing (≥130 IU/kg) administered on a daily basis.
- No adverse events related to rFVIIIFc were reported.

Dr. Pipe presented interim results from the verITI-8 Study, an ongoing global, prospective study of rFVIIIFc for first-time ITI therapy in patients with severe hemophilia A and high-titer inhibitors. ITI success or tolerization was defined as achieving all of the following: negative Bethesda titer at 2 consecutive visits; normal incremental recovery of at least 66% at 2 consecutive visits; and normal PK, defined as rFVIIIFc half-life of at least 7 hours. To date, 6 of 15 patients receiving 200 IU/kg/day of rFVIIIFc have achieved success. The median time to tolerization has been rapid: half a month to achieve a negative Bethesda titer; 1.4 months to achieve normal recovery; and 2.5 months to achieve normal half-life.

Safety of polyethylene glycol (PEG) containing products

JOHN MURPHY, PHD, RARE DISEASE RESEARCH UNIT, PFIZER

Dr. John Murphy presented a summary of four PEGylated clotting factor products: Adynovate/Adynovi (Takeda), Jivi (Bayer), Esperoct (Novo Nordisk), and Rebinyn/Refixia (Novo Nordisk). These therapies have mostly all been approved for episodic treatment, surgery, and prophylaxis in North American and Europe; with the exception of Rebinyn, which is not indicated for prophylaxis in the United States, and Jivi, which is not indicated for surgery in Canada. There are also differences in the age cohorts covered under the licensing approvals in Europe (patients 12 years of age and above), the United States (all ages; except Jivi, which is not indicated in children), and Canada (varying cohorts per therapy). He reviewed the rationale of the regulatory process and how it has produced differential outcomes, and concerns about chronic use of PEG products.

Vacuolation has been observed in multiple non-clinical studies of PEGylated products outside of hemophilia therapies and concern remains. These vacuoles may be an adaptive response by cells to PEG accumulation. In non-clinical studies, vacuoles have been seen in renal tubular cells, macrophages, and epithelial cells in the choroid plexus. This observation is of particular concern as the choroid plexus is the source of cerebral spinal fluid (CSF) and a component of the blood–CSF barrier; consequently, disruption may lead to neuronal impairment, although this outcome has not been seen to date.

PEGylated coagulation factors have been well tolerated in both clinical and non-clinical studies. Histological findings of PEG accumulation and vacuolation are possible concerns for lifelong chronically administered drugs; however, the doses of PEGylated factors are generally significantly below doses at which this is seen. Long-term consequences and clinical hallmarks of PEG accumulation are not known. The European Medicines Agency, based on this risk and advice from the Safety Working Party of its Committee for Medicinal Products for Human Use (CHMP), has taken a cautious approach to benefit–risk assessment of such PEGylated products in children: more data are needed and the risk of vacuolation must be addressed before longer-term clinical trials can be carried out in pediatric populations. The U.S. Food and Drug Administration has licensed all four PEGylated products for adults and children; with the exception of Jivi, which is only indicated for patients 12 years of age and above, due to a high frequency of anti-PEG IgM antibodies seen in the pediatric population resulting in hypersensitivity and loss of efficacy. It remains unclear why this is seen in Jivi but not in other products.

Impact on per capita FVIII usage when more countries are buying EHL products and emicizumab

JEFFREY S. STONEBRAKER, PHD, NORTH CAROLINA STATE UNIVERSITY, RALEIGH, NORTH CAROLINA, USA

In years past, per capita was used to measure health provision in hemophilia care, and standard-half-life international unit per capita has been the standardized unit of measurement for hemophilia treatment, said Dr. Jeffrey Stonebraker. However, the use of extended half-life factor products and emicizumab (Hemlibra) is increasing, especially in high-income countries, and the new product mix makes it difficult to measure different hemophilia treatments using a single universal metric and to understand the different usage levels and costs. Dr. Stonebraker described the development of an updated method for measuring hemophilia treatment and product usage using a single metric, taking into account the different product types and varying treatment modalities around the world for hemophilia A.

A correction adjustment approach was used to convert EHL to SHL IUs: prophylaxis data on observed SHL use and manufacturer's prescribing information for SHL and EHL products were used to calculate annual treatment using dose and frequency and determine range of annual treatment, then used to calculate the correction adjustment to convert EHL to SHL equivalency. The investigators determined a correction adjustment of 1.0 for converting EHL to SHL IUs; and a correction adjustment of 70 IU/mg for converting emicizumab to SHL IUs.

Data from the WFH Annual Global Survey from 2001 to 2018 was used to forecast the anticipated increase in global availability and usage of SHL IUs per capita moving forward, using data from countries where EHL products and emicizumab have been on the uptake. Comparison of a linear forecasting of SHL use with a correction adjustment approach showed an overlap of ranges, suggesting no significant difference between the IUs in SHL and EHL products for the treatment of hemophilia A. This correction adjustment approach can be used to convert EHL and emicizumab products to SHL IUs. There is a strong need for real-world observational data of EHL products and emicizumab in the treatment of hemophilia A.

Panel discussion

Dr. Glenn Pierce asked whether a patient showing a long half-life with SHL would have even longer half-life with EHL Dr. Iorio reported that of 700 patients enrolled in WAPPS, 300 patients are doing better on SHL factor instead of EHL. Mr. O'Mahony inquired whether that is due to the importance of peaks as well as troughs. There is great variability across EHL concentrates and the reasons why an extension method works for some patients and not others are not well understood, Dr. Iorio replied. Dr. Len Valentino (USA) emphasized the need for clinical correlation of the data on EHL factor products and emicizumab with the clinical outcomes in patients, and the need for better joint outcome studies on these new therapies.

Mr. Skinner noted that in a tender process, a government or Ministry of Health would see SHL and EHL products as being relatively equal and would not be able to tell the difference between PEGylated and nonPEGylated products. What would be the advice? Should product purchase be based on price alone at that point? In Canada, WAPPS data is provided to Canadian Blood Services to show the current usage of hemophilia therapies in terms of units, frequency of treatment, and variations in treatment, Dr. Iorio said.

Dr. Pipe said the NHF staunchly supports open access to all products and decision-making based on the personal benefit for individuals; the U.S. perspective is that price as sole determinant takes away from the clinician and patient's ability to decide together. Mr. O'Mahony noted that tender processes must include multi-criteria analyses of safety, efficacy, and quality. Beyond price alone, health authorities and payers must consider the value conferred at that price. Ireland has switched from

SHL to EHL factor products based on efficacy; outcome data show significant impacts in terms of improved quality of life. The challenge is the absence of outcome data before the product switch.

NON-FACTOR PRODUCTS

CHAIR: DR. MAGDY EL EKIABY, SHABRAWISHI HOSPITAL, BLOOD TRANSFUSION CENTER, GIZA, EGYPT

Non-factor replacement therapies have very recently come into clinical use. Dr. Magdy El Ekiaby noted some key questions: What does the bleeding disorders community need to know about these products? What is not known? What needs to be known? Most data are from clinical trials but the products are now in use in real life.

Hemlibra, fitusiran and anti-TFPI: measurement and assessment of these non-factor products

PETER LENTING, PHD, FRENCH NATIONAL INSTITUTE OF HEALTH AND MEDICAL RESEARCH (INSERM), PARIS, FRANCE

Dr. Peter Lenting began by comparing the currently available FVIII products and non-factor replacement therapies and describing their similarities and differences. The main contrast with FVIII concentrates is that non-factor replacement products can be used in hemophilia patients with or without inhibitors, have no troughs or peaks, and can be administered subcutaneously. They also demonstrate relative efficacy and a reduction in annualized bleeding rates. Two important questions with non-factor replacement therapies are how to monitor target protein in clinical laboratories and determining their factor equivalence.

Dr. Lenting reviewed some of the current assays available for monitoring the specific target proteins. For FVIII, these include the one-stage clotting assay, chromogenic assay, ELISA, and others. For emicizumab (Hemlibra) there is now a diluted one-stage clotting assay and a chromogenic assay using human FIXa/FX. Fitusiran is assessed using thrombin- or FXa-based chromogenic assays and ELISA. For anti-TFPI agents, options are ELISA, a diluted prothrombin time-based assay, and a TF-dependent chromogenic assay. A key challenge is lack of assay consistency related to the different mechanisms of action underlying different non-factor replacement therapies. Factor activity assays are based on a deficiency of FVIII; thus in these assays, FVIII should be the limiting factor, while FIXa should be in excess. In each type of assay, the amount of FIXa that is generated is different, as it depends on the composition of the reagents, the activating agent used, and other factors. Since the action of emicizumab is limited by the amount of FIXa and phospholipids that are available, it will react differently in each type of assay.

New therapeutic approaches in hemophilia A are associated with marked reduction in annualized bleeding rates, and monitoring these therapies is relatively straightforward using existing or adapted activity or antigen assays. The patient's response to treatment can be monitored via global assays, including thrombin generation assays. A true FVIII equivalent cannot be derived from in *vitro* assays, as illustrated by the variable response for emicizumab in the different assay systems. Dedicated animal models may lead to better understanding of the *in vivo* hemostatic potential of these agents under different types of conditions.

Hemlibra clinical assays

ANNETTE BOWYER, PHD, SHEFFIELD HAEMOPHILIA AND THROMBOSIS CENTRE, U.K.

The current state of knowledge on emicizumab (Hemlibra) clinical assays is that the activated partial thromboplastin time (aPTT) is significantly shortened, aPTT-based one-stage FVIII clotting assays are artificially increased, and chromogenic FVIII assays may be insensitive or sensitive to the presence of emicizumab, said Dr. Annette Bowyer. She shared results from her laboratory showing the performance of these tests in hemophilia A patients.

The one-stage assay with plasma calibrators cannot be used in the presence of emicizumab; however, emicizumab calibrators can be used in a modified one-stage assay to measure drug concentration. The other assay in common use is chromogenic. It is important to note that the reagent source can have significant variations. Different assays used on the same patients have demonstrated variations between assays in different types of patients. Chromogenic assays with human FX are sensitive to emicizumab, therefore, they can be used to measure drug presence. Chromogenic assays with bovine FX are insensitive to emicizumab, therefore, they can be used to measure rFVIII treatment and anti-FVIII inhibitors. Some patients developed anti-drug antibodies to emicizumab. There is no routine hemostasis assay to measure the presence of these antibodies. Several investigator groups are working on developing such assays.

Update on adverse events: Hemlibra, FEIBA, NovoSeven

MICHAEL MAKRIS, MD, UNIVERSITY OF SHEFFIELD; SHEFFIELD HAEMOPHILIA AND THROMBOSIS CENTRE, SHEFFIELD, U.K.

Dr. Michael Makris said it is difficult to compare emicizumab (Hemlibra), activated prothrombin complex concentrate (aPCC, FEIBA), and recombinant activated coagulation factor VII (rFVIIa, NovoSeven), especially due to the new and ongoing evidence being reported on all three products. Furthermore, it is difficult getting comparable data on the products since some have been on the market much longer and the reporting of product use varies for each type.

Dr. Makris shared data on injection site and severe allergic reactions. Emicizumab injection site reactions were reported in the HAVEN 1-4 clinical studies; allergic reaction occurred in one patient at the Sheffield centre. These reactions are rare with aPCC and expected to be around 1-3 cases per 10,000 patients. There are only case reports of these reactions with rFVIIa and no estimated rates.

Dr. Makris showed the adverse events reported from emicizumab in clinical use on the Genentech website (an equivalent is not available in Europe) and noted that the number of patients using emicizumab is dramatically increasing per quarter. Four cases of thrombotic microangiopathy (TMA) have been reported; all were associated with patients who were also treated with aPCC. Nine cases of thrombotic events related to emicizumab have also been reported but there is very little information on their precise nature. The rate of thrombotic events in emicizumab patients appears to be in the same range as in patients treated with rFVIIa or aPCC. Dr. Makris also shared data on thrombotic events and mortality with these products, while noting that it is too early to compare these small numbers. At this time, it is too early to know the differences in allergic reactions, thrombosis, and mortality between emicizumab, aPCC, and rFVIIa. Prospective pharmacovigilance is essential for all hemophilia treatments, but the key challenge is how to compare the products when the data are presented in different ways.

Subcutaneous administration of factors VIIa, VIII and IX and immunogenicity

JOHNNY MAHLANGU, MD, UNIVERSITY OF THE WITWATERSRAND; CHARLOTTE MAXEKE JOHANNESBURG HOSPITAL, SOUTH AFRICA

Subcutaneous administration of factor products is an attractive alternative to intravenous infusion, which can involve frequent, burdensome treatment and is associated with challenges such as inadequate venous access in young pediatric patients, infection, and thrombosis with long-term treatment, Dr. Johnny Mahlangu said. Subcutaneous non-factor therapies offer several advantages for patients: self-administration, convenience, quick and easy injection, and cost effectiveness. The therapeutic advantages include: long biological half-life, the ability to achieve much higher factor levels, and more stable and continuously protective levels. Furthermore, these therapies can be used to manage hemophilia patients with or without inhibitors. Disadvantages include injection site reactions, which have been seen in up to a quarter of patients and delayed exposure to clotting factor. Furthermore, these therapies can only be used for prophylaxis and not for treating acute bleeds.

Dr. Mahlangu reviewed subcutaneous FVII, FVIII and FIX clinical development programs in early phases of development. Early phase results indicate that subcutaneous administration has favourable pharmacokinetic, efficacy, and overall safety profiles. Immunogenicity with subcutaneous rFVIIa appears to be low, while subcutaneous rFIX shows comparable immunogenicity and quality to currently available intravenous rFIX products. These programs are progressing to phase 2 and 3 clinical development. Subcutaneous administration of rFVIIIa (N8-GP) was associated with high immunogenicity and high incidence of antibodies in previously treated patients (PTPs) with severe hemophilia A; further clinical development has been suspended. However, it is important to note that subcutaneous administration of clotting factors has the potential to address the current unmet needs with intravenous therapies, and immunogenicity in the early phases of clinical development is not always predictive of future immunogenicity.

Hemlibra use in newborns and infants

ASSAF BARG, MD, NATIONAL HEMOPHILIA CENTER AND THROMBOSIS INSTITUTE, TEL HASHOMER, ISRAEL

Dr. Assaf Barg described the experience in Israel treating infants and toddlers with emicizumab. The first patient was diagnosed with high-responding inhibitors following an allergic reaction to recombinant polyethylene glycol-based FVIII. IgE directed against various FVIII products was detected following this episode; there was no IgE against PEG, thus confirming the allergy was against the FVIII alone, and subsequent intradermal tests yielded wheal and flare with multiple recombinant and plasma-derived FVIII products. Since ITI was contraindicated, prophylaxis with emicizumab was initiated with successful results and the use of bypassing agents was dramatically reduced. The centre then extended emicizumab prophylaxis to a prospectively followed cohort of infants and very young children with hemophilia A and inhibitors (ranging from 2 months to 7 years of age). Clinical follow-up included documentation of any trauma, bleeding, or adverse event. Laboratory follow-up included global coagulation assays, rotational thromboelastometry (ROTEM), and thrombin generation (TG), prior to and during treatment.

All parents reported significantly improved quality of life with the convenient subcutaneous administration and home therapy. None of the patients experienced hemarthrosis or other spontaneous bleeds since treatment initiation. Only 4 of 11 patients were occasionally treated with rFVIIa for trauma. Two minor surgeries were safely performed without supplemental therapy, but another procedure was complicated by major bleeding. The administration of emicizumab prophylaxis resulted in a marked decrease of bypass agent consumption. Ten out of the 11 patients had received rFVIIa at a median monthly dose of 45 mg (dose range of 6-115 mg) prior to the initiation of emicizumab; following emicizumab prophylaxis, rFVIIa monthly doses ranged between 0-2 mg (median 0 mg per patient).

In one case, ROTEM analysis performed post-emicizumab loading when the patient was 3 months old yielded results showing near-normal values; however, subsequently the patient's circumcision resulted in major bleeding that required blood transfusions and rFVIIa with hospitalization in the pediatric intensive care unit. TG tests at the same time demonstrated an extremely low peak and endogenous thrombin potential (ETP). The post-circumcision bleeding in this patient despite near-normal ROTEM values suggests that TG may be the preferred global assay for hemostasis assessment in patients with hemophilia A and inhibitors treated by emicizumab.

It is possible that infants show more rapid clearance of emicizumab. TG was re-examined when the patient was 6 months old and the results showed marked improvement correlating with physiologic developmental hemostatic changes observed at infancy. Newborns and young infants display physiologically reduced levels of vitamin K-dependent coagulation factors, including FIX, which may impair emicizumab's mode of action. Their experience suggests that emicizumab prophylaxis is effective and safe even in very young children. However, vigilant attention is warranted when treating infants and in surgical settings. TG may more accurately reflect the hemostatic state than ROTEM. Regardless, caution is advised when interpreting global assay results in emicizumab-treated patients, and correlation with the clinical setting is essential.

Discussion

Dr. Pipe noted that there is probably no anticoagulant that provides perfect protection from breakthrough thrombosis and complete absence of bleeding, and it is unlikely that any procoagulant could be developed that would perfectly protect from all bleeds and have no risk of thrombosis. What information should be sought in the safety reports? Dr. Makris replied that it is important to know where the ceiling is, the dose at which the maximum benefit is achieved and above which there is risk of serious adverse effects. It may then be possible to give a lower dose that is not associated with thrombosis, which may be just a dosage effect; however, the safety margins of the different products are not clear.

Dr. Pipe said that an agent with a very narrow safety margin would be impractical to use. However, new agents should not necessarily be abandoned because of risk of certain types of bleeding complications; there will likely always be a scenario where the physiology of a patient combined with the procoagulant precipitates some thrombotic risk. A key challenge in this new era is learning how to use the new therapies safely and properly; safety reports should be used to guide safe administration and concomitant use with all the other products. Dr. Makris agreed, adding that the safety margins are not the same among different age groups. The agents are now being used to treat patients of all types and ages, including older individuals with higher risk of small thrombosis, whereas patients at risk of thrombosis were excluded from clinical trials. Dr. Prasad Mathews (USA) expressed concern about the use of emicizumab in infants and cautioned that more information on its use in infants and babies before using it carte blanche in young babies.

POINT OF CARE DIAGNOSIS

CHAIR: CEDRIC HERMANS, MD, CATHOLIC UNIVERSITY OF LOUVAIN, LEUVEN; SAINT-LUC UNIVERSITY HOSPITAL, BRUSSELS, BELGIUM

Increasing diagnosis and identification of people with hemophilia and other inherited bleeding disorders are key aspects of the WFH's overall ambition of "Treatment for All," Dr. Cedric Hermans said. Critically important to achieving these goals are clinical awareness, clinical suspicion, and ability to recognize patients with inherited bleeding disorders. Healthcare providers need to be able to recognize bleeding symptoms, family history, musculoskeletal problems, and other signs suggestive

of a bleeding disorder. There have been cases in some countries in which patients have been labelled with arthropathy and only learned of their underlying disease many years later. To confirm diagnosis, laboratory testing is required to identify and confirm the coagulation defect. Ideally, standard coagulation tests should be performed in a central laboratory, but this is sometimes difficult in real life. Point-of-care (POC) devices could offer new and more convenient modalities for diagnosis and monitoring of bleeding disorders.

POC assays – summary of state of the art on POC assays

PIERRE TOULON, PHD, CÔTE D'AZUR UNIVERSITY; PASTEUR UNIVERSITY HOSPITAL, NICE, FRANCE

Dr. Pierre Toulon described the use of point-of-care devices for hemostasis testing, focusing on aPTT as a POC global screening assay for FVIII:C and FIX deficiency. Advantages of aPTT as a POC global assay for FVIII and FIX measurement are that it is already available either for capillary blood sample or citrated blood, and it is affordable with a list price of around €7.00 per test. Potential limitations are that it is a global assay, not specific to FVIII:C/FIX deficiency; the need for confirmatory measurement of FVIII:C or FIX in the case of a prolonged test result; and sensitivity to low levels of FVIII:C and FIX has not been validated so far as the assay was not developed for these indications. Stability of test strips in high temperature and humidity conditions may also be an issue.

A rapid semi-quantitative solid-phase immunochromatographic assay for FVIII:C has been developed at the National Institute of Immunohematology in India. A FVIII:C specific antibody is conjugated with colloidal gold, applied to an acetate cellulose chromatography membrane strip, and placed in a plastic single-use device. A 50-µL plasma sample is dispensed into a well in the device; FVIII:C antigen in the sample will react with the immobilized gold-conjugated specific antibody. FVIII:C above around 5 IU/dL (5%) will cause the formation of a coloured line indicating a positive test result. The kits can be used in any primary healthcare centre without the need for any technical expertise or expensive equipment. Advantages are that the device is already developed and prototypes are available for field study, and it is affordable—the expected list price is less than US$1.00 per test. Potential limitations include the need for centrifugation of plasma collected in citrated tubes. Sensitivity for detection of low FVIII:C levels has to be more precisely defined and independently validated. Stability of test strips in high temperature and high humidity conditions as well as inter-observer variability may also be concerns.

Overall, these types of POC coagulation testing devices show promising potential for hemophilia diagnosis in remote areas, however, there are key issues to be addressed surrounding availability, cost, device and cartridge stability in high temperature and humidity, and performance in real life, he concluded.

FVIII point-of-care monitoring device

EUGENE CHAN, MD, RHEALTH, DNA MEDICINE INSTITUTE, INC. MASSACHUSETTS, USA

Dr. Eugene Chan presented rHealth's point-of-care FVIII testing device, which is capable of analyzing blood samples collected by finger prick (capillary microvolume sampling < 20 µl) or venous access. The device uses rHealth blood sensor technology to perform a quantitative fluorogenic assay capable of detecting FVIII levels ranging from 0.5% to 200% levels and producing highly accurate results within 15 minutes. It provides medical providers with the ability to test and promptly diagnose hemophilia A without requiring laboratory services, and for individuals with hemophilia A to self-test and monitor their FVIII levels. The device contains a mobile application and Bluetooth

technology for sending results to a treatment centre or physician, thereby enabling real-time clinical consultation and decision-making.

The easy-to-use POC FVIII testing device offers a number of benefits. It simplifies and standardizes testing and eliminates human error; enables early inhibitor detection; and supports individualized treatment based on the patient's pharmacokinetic profile to prevent breakthrough bleeding. It will also make it possible to increase diagnosis of hemophilia A in developing countries, where the majority of people with hemophilia remain unidentified and undiagnosed.

Dr. Chan noted that the NHF Medical and Scientific Advisory Council has recommended the adoption of chromogenic factor assays due to limitations and shortcomings of aPTT-based assays including the greater variability of results, especially with factor activity levels in the lower range, i.e., severe factor deficiency; inadequate sensitivity screening for mild factor deficiencies in some test conditions; and greater variation in results for extended-half-life factor therapies. rHealth's two-stage fluorogenic assay has similar steps as the chromogenic assay and uses a highly active fluorogenic peptide discovered with this assay, which offers better sensitivity and dynamic range than the chromogenic assay, Dr. Chan said. The next steps are to advance clinical development in collaboration with the WFH and Boston Children's Hospital via a U.S. National Institutes of Health (NIH) grant, and to obtain regulatory approvals for the device and assay.

FVIII monitoring device

WAANDER L. VAN HEERDE, PHD, ENZYRE, NIJMEGEN, THE NETHERLANDS

Enzyre is developing point-of-care diagnostic technology for coagulation testing, with a specific focus on the potential applications to treat or prevent life-threatening bleeding in several fields: hemophilia and other bleeding disorders, critical care settings, acute trauma situations, and management of medication-induced bleeding. The goal is to expand capacities in coagulation testing and related acute care all around the world, especially in developing countries and in remote areas, by bringing the lab to the patient to obtain better and more detailed information and thereby enable immediate treatment and personalization of care, Dr. Waander van Heerde explained. The device will also allow people with hemophilia to self-test their coagulation levels at home or elsewhere outside the hospital setting, to monitor their coagulation status in real time and potentially optimize their treatment accordingly.

Enzyre developed the EnzyPad and EnzyCard to measure multiple relevant blood coagulation parameters in parallel, including FVIII, FIX, and thrombin generation. The system consists of a blood sensor device which uses chemiluminescent detection to measure FVIII and FIX activity levels in a small blood sample (10 µl); EnzyPad reusable processor which interacts with a mobile phone to transfer data immediately to the patient's physician; and a disposable EnzyCard cartridge for testing specific reagents.

ENSURING ACCESS TO AFFORDABLE TREATMENT PRODUCTS AND HUMANITARIAN AID

CHAIR: AMPAIWAN CHUANSUMRIT, MD, MAHIDOL UNIVERSITY; RAMATHIBODI HOSPITAL, BANGKOK, THAILAND

Dr. Ampaiwan Chuansumrit opened the session with an audience poll on whether a national tender is the best way to procure therapy; 61% responded yes and 39% responded no. Polled again at the end of the session, 76% responded yes and 24% responded no.

The impact of innovation on access to hemophilia therapy

PATRICK ROBERT, PHD, MARKETING RESEARCH BUREAU, ORANGE, CONNECTICUT, USA

Mr. Patrick Robert gave an overview of the evolution of the hemophilia treatment market and impacts of new innovations on access from 1992 to today. Global plasma-derived FVIII sales from 1992 to 2018 increased from 1.9 billion to 4.4 billion IUs. The introduction of recombinant products in the 1990s increased the global supply of FVIII and FIX far beyond what could be made from plasma and contributed to increased access to therapy for many patients around the world. Data from 1992 to 2018 show the increasing use of recombinant FVIII globally, particularly by high-income countries; at the same time, as recombinant use increased, plasma-derived products became more available to less developed countries. The data also show the impact of humanitarian aid products from the WFH and other organizations, which raised the factor usage trends in Asia Pacific and other regions with lower-income countries.

Since the first recombinant FVIII products were approved in 1992, the global market has become 200% larger than it would have been with just plasma-derived products. In recent years, the availability of a wide variety of new recombinant and extended half-life factor products in high-income countries has pushed down the prices of standard half-life recombinant products and plasma-derived products, and increased the availability of therapies, particularly in under-served, low-income countries. Without the availability of recombinant FVIII, the plasma-derived industry would not be able to meet the global demand for FVIII therapies. Similar trends can be seen for worldwide FIX demand. Since the introduction of recombinant FIX in 1997, the global market has become over 100% larger than it would have been with only plasma-derived products.

Increases in production volumes, through higher production volumes of standard recombinant products along with the introduction of new products, have allowed expansion of the market internationally by shifting plasma-derived products from high-income to low-income countries. Innovations in the production process of recombinant factors have reduced their manufacturing costs. Technological innovations have brought higher yields in cell production systems, larger growth medium tanks and other economies of scale, implementation of new factor VIII sequences that are easy to produce (e.g., single chain), and EHL products requiring fewer units for prophylactic treatment than SHL products. The new recombinant EHL products introduced in recent years have further increased the supply of clotting factors. In addition, the new generation of recombinant non-factor replacement and monoclonal antibody products are less expensive to manufacture than conventional recombinant FVIII and FIX products, and are expected to increase the volume of therapies available worldwide.

Gene therapy administered in a single infusion that provides long-term, possibly lifelong treatment has the potential to radically change hemophilia treatment and cause a paradigm shift in hemophilia care. Some gene therapy products reportedly reduce factor usage by over 96%. Gene therapy may be particularly indicated for patients who have limited access to healthcare services. However, it must overcome many hurdles before it becomes standard of care. These include cost, low production capacity, pre-existing antibodies to gene therapy vectors, ineligibility of inhibitor patients, and fall-off of factor activity levels.

WFH Humanitarian Aid

ASSAD HAFFAR, MD, MEDICAL AND HUMANITARIAN AID DIRECTOR, WORLD FEDERATION OF HEMOPHILIA

Despite the tremendous improvement in hemophilia care in the developed world, the reality has not changed much in the developing world, where 70-75% of people with hemophilia in the developing world remain undiagnosed and the majority of those diagnosed still have no access or very limited access to treatment, Dr. Assad Haffar said. In 2015, WFH initiated an expansion of its Humanitarian Aid Program with the aim of increasing WFH donations of hemophilia treatment products to meet the increased need in developing countries, and expanding the program's scope beyond ad hoc donations distributed for the treatment of acute bleeds, emergencies, and limb- or life-saving surgeries. The main goals were to make donations more predictable in terms of quantity, timeline, and shelf life; increase humanitarian donations and reach an additional 60-65 countries; demonstrate to health authorities the value of treating hemophilia with clotting factor concentrates; leverage the program to motivate governments to increase investments in hemophilia care; and establish sustainable agreements with recipient countries.

During the 3-year expansion period, the WFH substantially increased the volume of humanitarian aid donations, enabling healthcare professionals to fully treat patients with bleeding disorders according to international standards and the WFH treatment guidelines. In addition to acute bleeding episodes and life-threatening surgeries, healthcare professionals are now also able to perform corrective surgeries and procedures; provide prophylactic treatment, including low-dose prophylaxis for children under 4 years of age; and provide immune tolerance induction therapy for patients with inhibitors. The program's reach increased exponentially, from 3,767 people with hemophilia receiving emergency life-threatening treatment in 2015 to 18,458 patients receiving treatment in 2018 for acute bleeds, surgeries, and prophylaxis.

The increased donations and availability of treatment in developing countries have led to increased outreach and diagnosis as well as increased medical training on optimal treatment of bleeding episodes, prophylactic treatment, corrective surgeries, and other invasive procedures (e.g., synovectomy, circumcision), and the diagnosis and management of inhibitors. It has also allowed regional cooperation in diagnosis and management; with cases such as the transfer of emergency products from Brazzaville to Kinshasa for a child with intracranial hemorrhage, and arrangements for a patient in Yemen to travel to India to receive specialized care for intra-abdominal hemorrhage. Outreach and training initiatives in Nigeria, Myanmar, Armenia, Senegal, and Gambia have demonstrated the positive outcomes of introducing treatment products and healthcare training in low-resource countries. Since its inception, 106 countries have received humanitarian aid via the WFH. Dr. Haffar thanked the sponsors of the WFH Humanitarian Aid Program who have made all of these advancements possible.

GAP update

ALAIN BAUMANN, CEO, WORLD FEDERATION OF HEMOPHILIA

Mr. Alain Baumann presented an overview and update on WFH's Global Alliance for Progress (GAP) program launched 16 years ago to foster partnerships and help develop sustainable national care programs in developing countries; and close the gaps in treatment and care, and between the estimated and identified number of people with bleeding disorders, the number of people born with hemophilia and those who reach adulthood, and the need versus the availability of treatment products.

The GAP program has involved 33 countries to date, with 15 active partnerships in 2018 and MOUs signed with 3 countries this year. Patient organizations, healthcare providers, and government work together to accomplish key goals. The WFH collaborates with each country for 5 years, helping set

clear objectives and providing all the means to get there. The impacts are measured in different ways: identification and diagnosis of patients, government support for care delivery, access and availability of treatment products, training of multidisciplinary healthcare teams, and capacity building of patient organizations. In 2018, GAP countries identified and diagnosed 866 new individuals with hemophilia, 278 new individuals with VWD, and 402 new individuals with rare bleeding disorders. In addition, about 800 hemophilia team members and regulators and similar numbers of patients and patient advocates participated in education and training workshops. Close to 500 million IUs in product supply were purchased.

In its first decade (2003–2012), GAP attained its goal to identify and/or diagnosis an additional 50,000 people with hemophilia in 10 years. The goal for the second decade is to identify an additional 50,000 people with inherited bleeding disorders by 2022, including a target of 25,000 new cases in the world's least developed countries. Alongside, the WFH works with the Ministry of Health in each GAP country to establish a national care program, an HTC or HTC network, and national patient registry; and to increase the budget and procurement of clotting factor concentrates and other treatment products for hemophilia and other inherited bleeding disorders.

In total over the years, the program has achieved a cumulative increase in product supply of 6.185 billion IUs in GAP countries. GAP has also increased access and availability of treatment, as reflected in significant increases in factor usage measured in IUs per capita. Nonetheless, there remain substantial gaps. In January 2020, the WFH will launch its new GAP Next Generation Program, which will synergize GAP initiatives with an expanded WFH Humanitarian Aid Program and the WFH World Bleeding Disorder Registry (WBDR). Mr. Baumann thanked WFH's GAP partners for their vital support: visionary partner Takeda, leadership partner CSL Behring, and collaborating partners Bayer, Biotest, Kedrion, Pfizer, Sanofi Genzyme and Sobi.

Tenders and procurement strategies for access to treatment

BRIAN O'MAHONY, IRISH HAEMOPHILIA SOCIETY, DUBLIN, IRELAND

Mr. Brian O'Mahony gave an overview of disparities in access and cost of treatment in countries around the world. Access depends on treatment protocols, organization of care, economics, and effective advocacy. Cost depends on factors such as what prices the market will bear; the country's national economy, healthcare budget, and purchasing system; and reference pricing. Other factors include competition, the number of products registered and licensed, and additional cost points such as distributor fees, handling fees, and taxes.

Strategies to improve treatment access include implementation of an open, fair, and transparent procurement system with the involvement of hemophilia clinicians and expert patient representatives in the process; removal of unnecessary costs or steps (e.g., distributor margins, handling fees); recognition of disparities in taxation of products, whereby valued-added tax (VAT) is applied to recombinant products but not to plasma-derived products; and economies of scale (e.g., multi-year commitments and larger purchases for the entire country). In Ireland, tender processes from 2002 to 2018 avoided €175 million in costs compared to the previous procurement system, which in real value equates to €275 million in cost savings including €22.74 million in costs avoided in terms of handling fees and taxes on fees. Importantly, the budget was not decreased; the theoretical savings were used to increase the supply and quality of products being purchased and a proportion of the savings reinvested in comprehensive care facilities and infrastructure. Factor usage in Ireland in 2002 was 3.7 IUs SHL FVIII per capita; in 2018, usage was 10.7 IUs EHL FVIII per capita. Ireland is the first country to switch all patients to EHL products.

From 1994 to 2014, recombinant factor concentrates were significantly more expensive than plasma-derived factor concentrates. However, the availability of EHL products has led to price competition among recombinant SHL products and decreases in unit cost of SHL recombinants in many countries. Likewise, aggressive marketing of EHL products has led to increasing competition among different EHL FVIII and FIX concentrates. The lower cost of recombinant products also put pressure on the prices of plasma-derived concentrates. This created an opportunity for emerging and developing countries to purchase products at lower unit cost and increase their factor supply with the same budget. The lowest reported cost is €0.06 per IU of plasma-derived FVIII and €0.12 per IU of recombinant FVIII. Taking advantage of these market circumstances requires an effective national tender or procurement system

COMMUNICATING ADVERSE EVENTS IN THE ERA OF SOCIAL MEDIA

CHAIR: MICHAEL MAKRIS, MD, UNIVERSITY OF SHEFFIELD; SHEFFIELD HAEMOPHILIA AND THROMBOSIS CENTRE, SHEFFIELD, U.K.

Sense, nonsense, and science

JOE SCHWARCZ, MD, MCGILL OFFICE FOR SCIENCE AND SOCIETY, MONTREAL, CANADA

Dr. Joe Schwarcz noted that although communication of adverse events in the era of social media is a current issue, it is not a new challenge. In hemophilia, it is well known that Alexei Nikolaevich (1904-1918), the last heir apparent to the throne of the Russian Empire, was born with severe hemophilia. By some accounts, "healer" Grigori Rasputin may have gained influence within the royal courts through his apparent ability to control the bleeding, particularly when Alexei had life-threatening hemorrhages. It is said that Rasputin halted the use of acetylsalicylic acid (Aspirin). Introduced in 1899, Aspirin was used to treat fever, pain, and inflammation but would have worsened Alexei's hemarthrosis due to its then unknown effects on coagulation; the drug's blood-thinning properties were only discovered in 1950.

Today, similar problems are encountered with new types of drugs. The public quickly learn from social media, radio, television, and the Internet when bad news emerges. For example, in 2018, there were robust social media discussions in the hemophilia community about the deaths of patients treated with emicizumab. The manufacturer informed patient organizations of the deaths in March 2018, maintaining that they were not related the drug but giving no details on cause. Concerns remained heightened. Investigations later yielded scientific evidence that some of the deaths were unrelated to emicizumab. Correlation is not the same as causation, Dr. Schwarcz noted. The onslaught of information from both dubious sources and legitimate sources in the scientific world often makes it difficult to keep up to date. Clear and timely communication of adverse events and accurate information are evermore critical.

NEW AND NOVEL HEMOPHILIA THERAPIES

CHAIR: RADOSLAW KACZMAREK, MD, WFH COAGULATION PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE CHAIR

Development of COX-2 inhibitors for hemophilia patients

STACY E. CROTEAU, MD, MMS, HARVARD MEDICAL SCHOOL BOSTON CHILDREN'S HOSPITAL, BOSTON, MASSACHUSETTS, USA

Dr. Stacy Croteau gave an overview of the development of cyclooxygenase-2 (COX-2) inhibitors, their safety profile in the general population and the hemophilia population, and their use in acute and chronic pain management for patients with hemophilia. COX-2 inhibitors (e.g., etoricoxib, celecoxib,

meloxicam, nimesulide, and others) are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) that specifically block COX-2 enzymes. They are used for treating conditions that cause inflammation, mild to moderate pain, and fever. Strategies for pain management in people with hemophilia with hemarthrosis and hemophilic arthropathy are generally based on starting with basic pain medication then, if not effective, progressing to increased strength medication: paracetamol/acetaminophen; COX-2 inhibitors; paracetamol/acetaminophen plus codeine; paracetamol/acetaminophen plus tramadol; then morphine. These medications are the main pharmacological options for hemophilic arthropathy. However, there is no validated plan for pain management in hemophilia.

Introduced in 1999, selective COX-2 inhibitors were successful in treating inflammatory conditions such as osteoarthritis and rheumatoid arthritis but concerns were raised about their adverse cardiovascular effects. Studies in 2004 and 2005 subsequently found the use of some selective COX-2 inhibitors were associated with significantly increased cardiovascular events with long-term use, leading in some cases to market withdrawal in some countries or from the worldwide market (e.g., rofecoxib, Vioxx), or requirements by regulatory authorities for manufacturers to make labelling changes to include precautions on potential risk of ischemic stroke, cardiovascular events, and other adverse events. A 2006 study on the efficacy and safety of etoricoxib (Arcoxia) in the treatment of hemophilic arthropathy in 102 patients at 8 centres in the U.S. and 7 international sites found it to be relatively well tolerated. However, adverse events (respiratory infection, headache, nausea, vomiting, coughing) occurred in 51% of patients in the 6-week base study and 63.5% of patients in the 6-month extension study; 2-5% of patients had serious adverse events (hemorrhoids, hemorrhagic duodenal/gastric ulcer, erosive gastritis, and subdural hematoma, hemorrhage, hypotension). Etoricoxib was withdrawn from the U.S. and some other countries, but is currently approved and sold in many countries worldwide. In 2017, the FDA granted orphan drug designation for rofecoxib as pain medication for hemophilic arthropathy.

In comparison to COX-2 inhibitors, traditional NSAIDs carry a higher risk of bleeding, particularly upper gastrointestinal (GI) bleeding; the risk is dose- and treatment duration-dependent. Both traditional NSAIDs and COX-2 inhibitors carry risks of thrombotic and renal bleeding complications, which are also dose- and treatment-duration dependent. COX-2 inhibitors are associated with higher risk of cardiovascular events and related mortality than traditional NSAIDs. A 2018 U.S. cross-sectional study found that despite common cardiovascular risk factors, older men with hemophilia had less disease and cardiovascular events, 10% compared to 17% of men of similar age in the general population.

COX-2 inhibitors are considered a suitable option for treatment of hemophilic arthropathy. Dr. Croteau presented a summary of recommendations on the use of COX-2 inhibitors in people with hemophilia:

- Balancing the pain control benefit vs. increased risk of adverse events, COX-2 inhibitors at the lowest possible dose and for the minimum treatment duration are the most reasonable options to control arthritic pain.
- Screening and eradication of Helicobacter pylori (H. pylori) infection is recommended prior to commencing COX-2 inhibitors.
- Regular blood pressure and renal function test monitoring are required once COX-2 inhibitors are commenced.

The use of COX-2 inhibitors as pain medication for hemophilic arthropathy expands the treatment options which would otherwise be limited to acetaminophen and opioids, and provides important benefits including better pain management and decreased risk of GI bleeding. However, it is

important to evaluate and monitor existing conditions (e.g., GI bleeding, cardiovascular or renal disease).

Anti TFPI antibody BAY 1093884

FRANCESCA FERRANTE, MD, BAYER

Dr. Francesca Ferrante gave an overview of Bayer's endeavour to develop an anti-TFPI antibody, BAY 1093884, for the treatment of hemophilia A, and the early termination of its phase 2 study due to thrombosis. The Phase 1 study demonstrated restoration of thrombin generation with no safety concerns. Non-clinical data and toxicology studies of BAY 1093884 suggested a favourable safety profile due to its high specificity towards TFPI with no off-target effects. Multiple pre-clinical and clinical studies suggested an additive, non-synergistic effect when BAY 1093884 was used in combination with bypassing agents or replacement factors. An increase in D-dimer was reported in all cohorts, as expected from the drug mechanism of action. No trend for decreasing fibrinogen levels, no decrease in platelet levels, and no clinically meaningful changes in anti-thrombin III, protein C, or factor V were observed.

During the phase 2 BAY 1093884 study, 3 patients developed thrombosis in the central nervous system. The first event occurred in a patient with mild hemophilia A diagnosed with inhibitors following surgery, who received 2 doses of BAY 1093884 a week apart. He was admitted to hospital several days later with dizziness, impaired vision, and headache; a CT scan revealed venous sinus thrombosis, which was successfully treated with an anticoagulant. As the patient had not received factor concentrates, the venous thrombosis was associated to the study drug. The second event occurred in a patient with severe hemophilia A, previously treated episodically. At 28 weeks of treatment with BAY1093884 (intermediate dose of 225 mg), he had experienced a single spontaneous bleed. However, he was subsequently admitted to hospital with dizziness and partial loss of vision. A CT scan determined ischemic stroke; the patient was treated and discharged after 1 week. The third thrombotic event occurred in a patient with severe hemophilia A previously treated episodically. At 9 weeks of treatment with BAY1093884 (high dose of 400 mg), the patient had experienced no spontaneous bleeding. However, a week later he was admitted to hospital with partial loss of vision in the right eye. A CT scan found retinal artery branch thrombosis. Bayer suspended dosing in all patients and after evaluation of the safety data from all patients, took the decision to early terminate the study.

Predicting safety without reference points is a major challenge in novel drug development. Dr. Ferrante noted that no laboratory abnormalities were observed; there was no hemolysis nor platelet consumption, and fibrinogen levels were within the safety range. The study found no correlation between dose and TFPI inhibition, nor between TFPI inhibition and efficacy. All 3 cases of thrombosis occurred in the central nervous system and no replacement factors or bypassing agents were involved; therefore, the events appear to be related to study drug. Further understanding of the impact of TFPI inhibition is needed.

Interim results from a phase 2b trial of etranacogene dezaparvovec (AMT-061:AAV5-Padua hFIX variant), an enhanced vector for gene transfer in adults with severe or moderate-severe hemophilia B

EILEEN SAWYER, PHD, VICE PRESIDENT AND HEAD OF MEDICAL AFFAIRS, UNIQURE

UniQure's etranacogene dezaparvovec (AMT-061) is an investigational gene therapy that consists of an AAV5 vector containing a codon-optimized Padua variant human factor IX gene with liver-specific promoter. Dr. Eileen Sawyer described interim results from the phase 2b study.

The phase 2b dose confirmation study in 3 patients showed 45% mean FIX activity at 36 weeks post-treatment with etranacogene dezaparvovec and reduction in bleeds and FIX replacement, with no spontaneous bleeding episodes. There were no clinically significant ALT elevations above the upper limit of normal after dosing. One patient experienced three isolated AST elevations above the upper limit of normal, which were resolved quickly without treatment or impact on FIX activity. None of the patients required immunosuppression and there was no loss of FIX activity and no FIX inhibitor development; 1 patient experienced 2 adverse events, possibly related to etranacogene dezaparvovec, which resolved without intervention. All 3 patients have discontinued prophylaxis.

The phase 2b dose escalation study in 10 patients with severe or moderate-severe hemophilia showed sustained dose-dependent increases in FIX activity. Overall, etranacogene dezaparvovec was safe and well tolerated, with stable FIX expression at 3-3.5 years of follow-up and no late emergent safety events. Follow-up of patients for 5 years minimum is ongoing.

Update on safety and efficacy of rFVIIIFc in pediatrics from recent clinical experience

STEFAN LETHAGEN, MD, PHD, SWEDISH ORPHAN BIOVITRUM (SOBI), STOCKHOLM, SWEDEN

Dr. Stefan Lethagen provided an update on rFVIIIFc in pediatric patients, including over 5 years of real-world clinical data. Low median annualized bleed rates (ABRs) have been recorded by pediatric patients receiving 1-4 years of individualized rFVIIIFc prophylaxis (median ABRs ≤2.0; median joint ABRs of 0.0; median spontaneous ABRs of 0.0). Clinical joint health score improvement was seen in all 42 pediatric patients on long-term rFVIIIFc prophylaxis up to 3 years. rFVIIIFc was evaluated for perioperative management in pediatric patients. There were 2 major surgeries and 26 minor surgeries performed; hemostatic response to treatment were all rated as "excellent" or "good." Clinical studies showed that rFVIIIFc is generally well-tolerated by pediatric patients; there were no cases of inhibitors during clinical studies in previously treated patients (PTPs) and adverse events were consistent with those expected in the hemophilia population. The safety profile of rFVIIIFc is supported by more than 5 years of real-world post-marketing experience.

The immature coagulation system in young children must be considered when new therapies are introduced. There is extensive experience of rFVIIIFc in previously treated pediatric patients, including safety and efficacy data from clinical studies in 71 pediatric PTPs (median age of 5 years) with a median of 3.5 years of cumulative treatment and post-marketing use (>5 years). For immune tolerance induction (ITI) emerging clinical data from 89 previously untreated patients (median age 0.6 years) suggest a lower risk of high-titer inhibitors and rapid tolerization in ITI. Clinical studies are ongoing to further elucidate the role of rFVIIIFc in immunomodulation. Efficacy and safety of rFVIIIFc is now well established in pediatric patients with hemophilia A.

Interim analysis of measures of efficacy, safety, and spontaneous bleeding events in the phase 2 open-label extension study of fitusiran in subjects with hemophilia A or B, with or without inhibitors

BAISONG MEI, MD, PHD, SANOFI GENZYME, CAMBRIDGE, MASSACHUSETTS

Dr. Baisong Mei presented an update on fitusiran, an antithrombin (AT) knockdown agent designed to lower AT levels with the goal of rebalancing hemostasis and promoting sufficient thrombin generation to prevent bleeding in people with hemophilia A or B, with or without inhibitors. Its development was based on the observation of milder bleeding phenotypes in people with hemophilia who have co-inherited thrombophilic markers, such as AT deficiency; this hypothesis has been supported by preclinical data and clinical studies. Fitusiran uses RNA interference (RNAi) technology to target AT in the liver; a chemically synthesized oligonucleotide blocks AT mRNA translation via the natural RNAi pathway. Conjugation to the N-acetylgalactosamine (GalNAc) ligand allows for efficient delivery to hepatocytes, the site of AT expression, via the asialoglycoprotein (ASGP) receptor. It is administered subcutaneously and allows for once-monthly prophylaxis in adults and adolescents with hemophilia A or B, with or without inhibitors.

Fitusiran shows potential for the prophylactic treatment of people with hemophilia A or B, with or without inhibitors. Previously presented data from the phase 1 study and phase 2 open-label extension (OLE) interim analysis of fitusiran showed a dose-dependent lowering of AT, increased TG, and decreased frequency of bleeding events in patients treated with fitusiran. In phase 2 and 3 studies, severe adverse events occurred in 12 of 34 patients enrolled. Four of the reported SAEs were considered related to the study drug: atrial thrombosis in a patient with hemophilia B and inhibitors; seizures in a patient with history of seizure disorder (CT and MRI negative for bleed and thrombosis); asymptomatic ALT and AST elevation in a patient with chronic HCV infection, which to led to discontinuation; and cerebral venous sinus thrombosis in a patient, which was fatal. Dr. Mei emphasized the importance of education to ensure that patients understand and adhere to their treatment protocols; close monitoring of bleed management and adverse effects; and guidelines on how to use factor and bypassing agents to treat spontaneous or traumatic bleeding while on fitusiran prophylaxis.

Long-term exposure to fitusiran in the phase 2 OLE study has shown a safety profile that is supportive of continued evaluation in phase 3 studies. Monthly dosing with fitusiran demonstrated a durable therapeutic effect including sustained AT lowering, increased TG, and low overall ABRs (median 0.97) and spontaneous ABRs (median 0.39). Most bleeds were located in joints and were mild in severity across all patient groups, whereas spontaneous and traumatic bleeds occurred more frequently in patients with inhibitors. The safety and efficacy of fitusiran is being evaluated in the ongoing global phase 3 ATLAS program.

Correcting blood disorders by implantation of ex vivo gene-modified allogeneic human cells shielded with biomaterials

DEYA CORZO, MD, SIGILON THERAPEUTICS

Dr. Deya Corzo presented a novel encapsulated cell therapy for hemophilia A by Sigilon Therapeutics called SIG-001. The investigational drug is being developed using Sigilon's Shielded Living Therapeutics technology, which combines a novel cell platform with a novel biomaterial platform. SIG-100 consists of a human cell genetically modified using a non-viral vector and optimized coding sequence for a B-domain deleted FVIII, and encapsulated within alginate spheres. The spheres are 1.5 mm in diameter and engineered using a proprietary mixture of small molecule–modified and unmodified alginates.

A key aim of the cell-based therapy is to enable delivery of controlled doses of therapeutic proteins without the need for immunosuppression and without the risks associated with gene therapy. Pre-clinical data of SIG-100 demonstrate both safety and efficacy in animal models. The findings include dose-dependent production of hFVIII, normalization of bleeding, and statistically significant reduction in bleeding time in hemophilia A mice relative to wild type mice. Studies also show sustained expression of hFVIII in NSG mice for over 6 months; and correlation between *in vitro* optimization and *in vivo* hFVIII activity levels, with sustained long-term expression at these levels *in vivo*.

SIG-001 has been granted orphan drug designation by the FDA. The first-in-human clinical trial is planned for 2020. Administration of SIG-001 will be intraperitoneally via short laparoscopy; the spheres can be re-dosed if needed. It has the potential to eliminate the need for regular factor and non-factor injections; provide consistent factor levels without the peaks and troughs observed with factor and non-factor therapies; expand use in pediatric patients; improve long-term outcomes; and combine with factors and gene therapy.

In vivo genome editing for hemophilia

MIKE CERTO, PHD, BLUEBIRD BIO, CAMBRDGE, MASSACHUSETTS, USA

Dr. Mike Certo presented bluebird bio's megaTAL gene editing platform and its new 3-year partnership with Novo Nordisk to develop an *in vivo* gene therapy for hemophilia A. The research will use bluebird bio's megaTAL technology, which is designed to silence, edit, or insert genetic components. The platform enables genome engineering and the generation of extremely active and highly specific and compact nucleases called megaTALs that are compatible with viral and non-viral cell delivery methods. The research will focus on FVIII gene correction and AAV-mediated knock-in of the FVIII transgene into the FVIII genome. The goal is to provide lifelong treatment, amenable to children and adolescents, with the ability to titrate to reach the desired FVIII activity level.

A megaTAL is a single-chain fusion enzyme that combines the natural DNA cleaving processes of homing endonucleases with the DNA binding region of transcription activator-like (TAL) effectors; the proteins are easily engineered to recognize specific DNA sequences. Each megaTAL is a fully orthogonal reagent and a single, monomeric component drives target recognition and cleavage. Its small size is compatible with *ex* and *in vivo* delivery modalities including AAV. The strategy is to use lipid nanoparticles (LNP) with megaTAL messenger RNA (mRNA) encapsulated in LNP. An AAV vector will serve as a donor template to knock in the megaTAL FVIII transgene. Scientific considerations include target site, expression level on a per cell basis, optimization of nanoparticle formulation, mRNA optimization, tolerability and production and manufacture. In mice, the megaTAL mRNA persistence decreases rapidly and is undetectable about 4 days after dosing. However, editing is durable and produces on-target liver insertion–deletion (INDEL) percentages at 6 months post-dose. Repeat dosing can be administered and appears to be titratable.

Three-year efficacy and safety results from a phase 1/2 clinical study of AAV5-HfVIII-SQ gene therapy (valoctocogene roxaparvovec) for severe hemophilia A (BMN 270-201 study)

BENJAMIN KIM, MD, MPHIL, BIOMARIN PHARMACEUTICAL, NOVATO, CALIFORNIA, USA

Dr. Benjamin Kim described three-year efficacy and safety results from phase 1/2 clinical studies of gene therapy with valoctocogene roxaparvovec (BMN 270-201) for severe hemophilia A. FVIII activity increased in a sustained manner after treatment with valoctocogene roxaparvovec. FVIII levels increased rapidly post-treatment with the highest dose of valoctocogene roxaparvovec and remained elevated. FVIII levels also increased post-treatment with the second highest dose but at a slower rate and lower level of elevation compared to the highest dose. FVIII levels begin to plateau in 2-3 years following gene transfer. Valoctocogene roxaparvovec was shown to achieve very positive clinical outcomes. There was a substantial reduction in treated annualized bleed rates (number of bleeding episodes requiring FVIII treatment in a year), with a 96% reduction in mean ABR in the highest dose cohort and a 92% reduction in the second highest dose cohort. All patients in the highest dose cohorts are no longer on prophylaxis and have 100% resolution in target joints; many of these patients had no bleeding episodes since treatment with valoctocogene roxaparvovec.

Accumulated data have shown valoctocogene roxaparvovec to have a favourable safety and tolerability profile. Rises in ALT levels have been the most notable treatment-related adverse event. ALT levels were mildly to moderately elevated around 8-16 weeks after dosing in most patients but were not associated with any clinical symptoms and subsided. No clinical issues were experienced due to corticosteroid use, which is used, as needed, in cases of increased ALT levels. There was no clinically significant impact on liver function. There was no relationship found between any immune responses and ALT elevations. Two patients experienced mild infusion reactions, which were managed by slowing the initial speed of the infusion and resolved within 48 hours with routine medical management. No patients have developed blood clots or inhibitors against FVIII. Valoctocogene roxaparvovec has been found to be effective for up to 3 years after treatment to date. These results are expected to be sustained throughout the phase 3 GENEr8-1 study of valoctocogene roxaparvovec.

DATA COLLECTION

CHAIR: SALIOU DIOP, MD, PHD, CHEIKH ANTA DIOP UNIVERSITY, DAKAR, SENEGAL

Dr. Saliou Diop opened the session with an audience poll on the condition(s) under which the prevalence of hemophilia will equal the prevalence of birth for hemophilia; 51% responded that all of these conditions must be met: all patients are accounted for and counted only once; treatment is available; and mortality rate of hemophilia is the same as the mortality rate of the population.

AGS 20th Anniversary: Updated estimates of prevalence and prevalence at birth in hemophilia

JEFFREY S. STONEBRAKER, PHD, NORTH CAROLINA STATE UNIVERSITY, RALEIGH, USA

Dr. Jeffrey Stonebraker reviewed the 20-year history of the WFH Annual Global Survey (AGS), which documents and tracks over time diagnosis, management and care, and the use of safe effective treatment products for all people with hemophilia, von Willebrand disease, and other inherited bleeding disorders. In 1999, 65 countries contributed data to the AGS; in 2018, 125 countries contributed their data. The number of identified people with bleeding disorders increased at an

annual growth rate of 6.4%. AGS data from 2002 to 2018 show increased factor use at the annual growth rate of 5.9% for FVIII and 3.7% for FIX.

Dr. Stonebraker then discussed newly updated estimates of hemophilia prevalence. Prevalence is the total number of identified cases of hemophilia in a population divided by the total number of males in that population at a given time. Prevalence at birth is the total number of males born with hemophilia among all males born in the population over a period of time (i.e., birth year). The concept of "life expectancy disadvantage" describes when the prevalence at birth is greater than its observed prevalence (i.e., people die earlier than the normal population, or excess mortality). The first estimate of global prevalence, 400,000 people with hemophilia worldwide, was made in the early 2000s; this estimate did not distinguish severe from moderate and mild disease, nor did it distinguish between the hemophilia A and B.

Upon the 20th anniversary of the AGS, the WFH Data and Demographics Committee undertook a reanalysis of the global prevalence and prevalence at birth of hemophilia, taking into account the large variability in hemophilia prevalence across countries and the negative effect of lower socioeconomic status. The results of the study by Iorio et al. were published in *Annals of Internal Medicine* in September 2019. The objective was to produce accurate estimates of the prevalence and prevalence at birth of hemophilia, separately for mild, moderate, and severe hemophilia; and for hemophilia A and hemophilia B. The study used meta-analytic methods and robust epidemiological data from established national patient registries (Australia, Canada, France, Italy, New Zealand, and the U.K.); and prevalence at birth estimates from the three most established registries (Canada, France, the U.K.). The new estimates indicate that the prevalence of hemophilia is approximately 3 times higher than previously estimated; the prevalence of hemophilia was estimated to be 21 per 100,000 males and the prevalence at birth was estimated to be 30 per 100,000 males. The expected number of people with hemophilia worldwide today is 1,125,000, of whom 418,000 should have severe hemophilia. The study also found significant life expectancy disadvantages for people with hemophilia in low-income countries. The study proposed total number of patients with hemophilia, proportion of patients with severe hemophilia, and the gap between prevalence and prevalence at birth as indexes of the maturity of national healthcare systems.

The updated estimates of hemophilia prevalence will encourage the WFH to continue its work to bring about improved diagnostic approaches to spur on new and more effective treatment to reduce the gap in life expectancy for hemophilia patients across all income levels; calculate markers of adequate care across the world to advocate for more equitable distribution of resources; and research the burden of disease for hemophilia.

EMA move from PMS to registries: Long-term follow-up

CAROLINE VOLTZ, EUROPEAN MEDICINES AGENCY (EMA)

Many novel therapies are under development in hemophilia including gene therapies and gene editing therapies with the potential to enable steady-state expression of endogenous factor VIII or factor IX within the normal range. The European Medicines Agency expects manufacturers of novel therapies to establish their favourable safety and efficacy profiles but a key challenge with rare diseases is that there are very limited numbers of patients enrolled in clinical trials.

For gene therapies, since hemophilia patients are regularly followed at specific centres or hospitals, there is an opportunity to use existing patient registries to collect gene therapy follow-up data for

marketing authorization and post-marketing measurements. However, additional safety endpoints and long-term efficacy data may be needed. Proposed safety endpoints include:

- hepatotoxicity (ALT, AST, bilirubin);
- immunogenicity (i.e., testing binding and neutralizing antibodies);
- use in peri-operative management (FVIII/FIX replacement therapy prescribed, actual IUs of FVIII/FIX replacement therapy used before, during, and after the procedure);
- surgical outcomes and surgeon rating of hemostatic control during the procedure to be collected after surgery.

It is also important to have post-marketing and long-term efficacy data. Proposed efficacy endpoints include:

- factor activity levels, factor consumption/treatment (monitored quarterly for first year then annually); number of bleeds during the previous year;
- annual quality-of-life assessment using the EQ-5D-5L and two disease-specific instruments, Haemophilia Quality of Life (Haem-A-QOL) and Patient Reported Outcomes, Burdens, and Experiences (PROBE);
- concomitant medications (dose and timing of the trigger should be collected when reporting adverse events).

Core data elements identified at the 2018 EMA workshop include: medical history, immunogenicity, safety monitoring (organ function, biochemistry), safety reporting, concomitant medications, quality of life data, medical history, and efficacy monitoring. The workshop also identified the need to be able to report other adverse events, for example, related to alcohol consumption, as there may be risks that are not yet known that will need to be reported.

Important considerations for national registry linkages to an international registry include:

- data analytics (e.g. patient identification code);
- legal aspects (e.g., agreement regarding ownership of registry data and compliance with national regulations (e.g., informed consent, data privacy);
- data source verification;
- escalation strategy in case of findings;
- harmonization of core data elements to ensure good quality baseline data.

Gene therapy presents an opportunity to have one common data set and a single international gene therapy registry. Collaboration is key for successful long-term follow-up of gene therapies, and patient and healthcare professional input, support, and participation are essential for the collection of good quality safety and efficacy data.

WFH World Bleeding Disorders Registry and World Hemophilia Gene Therapy Registry

BARBARA KONKLE, MD, UNIVERSITY OF WASHINGTON; WASHINGTON CENTER FOR BLEEDING DISORDERS, BLOODWORKS NORTHWEST. SEATTLE, WASHINGTON, USA

The WFH World Bleeding Disorders Registry is the only global registry that collects standardized clinical data on people with hemophilia around world. The WBDR is of value towards fulfilling several important purposes. On an HTC level, centres can use the WBDR to collect individual patient data, manage patient care, and assess outcomes after therapeutic interventions; this is particularly critical for centres that do not have a data management system for following patients. Then, through data sharing agreements, the centre's database can join with other centres locally and regionally, and/or

serve as the central database for a country or region. From a global standpoint, the data can be used to compare outcomes regionally and internationally and investigate important research questions arising from the data. The WBDR also has an international data integration component, whereby existing hemophilia registries can transfer their data directly into the global registry.

The minimal diagnostics data set consists of the date of diagnosis, hemophilia type, hemophilia severity hemophilia factor level, and disease history. The extended diagnostics data set includes genetic testing, blood type, and family history. The minimal clinical data set consists of bleeding events, target joints, treatments, inhibitor status, hospitalization, and mortality. The extended clinical data set includes adverse events, functional scales, co-morbidities, and quality of life scales. A pilot study was completed in December 2016 and launch of the extended data set took place in 2019. A collaboration with HTCs in the Czech Republic is underway, with a data linkage process enabling them to upload their national registry data directly into the WBDR. It is compliant with EU data protection laws. Each participating HTC owns their own data and can view and use their data at any time. An HTC cannot view the data of any other HTC; however, through a data sharing agreement, HTCs can combine their data. Enrolment now includes 37 countries participating, with 77 HTCs and a total of 3,844 hemophilia patients.

The World Hemophilia Gene Therapy Registry (GTR) is a newer project with the goal of building one global registry for all gene therapy patients from all countries. The objective is to collect long-term data to identify low incidence toxicities and variability and durability of efficacy. The GTR will be a separate database from the WBDR but will take advantage of the WBDR programs and components in place: the Data Quality Accreditation Program, data linkages from existing registries, the HTC training program, and investigator meetings. The WFH has established a multi-stakeholder steering committee, which keeps contact with the EMA and FDA in order to meet their requirements as well. The steering committee is also working collaboratively with the American Thrombosis and Hemostasis Network (ATHN) to make sure their data harmonizes with the WBDR.

GENE AND CELL THERAPY

CHAIR: GLENN PIERCE, MD, PHD, VICE PRESIDENT, MEDICAL, WORLD FEDERATION OF HEMOPHILIA

Gene therapy pipeline

Dr. Glenn Pierce opened the session with an overview of investigations into hemophilia gene therapy over the years and the development and status of current hemophilia gene therapy clinical and pre-clinical trials. In hemophilia A, numerous preclinical and phase 1/2 trials of AAV and lentiviral vectors are underway. Ongoing phase 3 FVIII gene therapy clinical trials include AAV5-FVIII/valoctocogene roxaparvovec (BMN-270 by BioMarin), AAV6-FVIII (SB-525 by Sangamo), and AAV LK03-FVIII (SPK-8011 by Spark). Other phase 3 clinical development programs will soon be initiated. In hemophilia B, phase 3 gene therapy clinical trials of AAV5-FIX Padua/etranacogene dezaparvovec (AMT-061 by uniQure) and AAV-FIX (SPK-9001 by Spark and Pfizer) are in progress.

Remaining barriers to curative AAV-based gene therapy requiring attention include: high cost and complexity of manufacture; high inefficiencies throughout; high AAV antibody seroprevalence; high inter-patient variability; unknown causes of transient transaminase elevations; and lack of data on AAV episomal persistence in adults. Currently, AAV- and non-AAV based solutions are the main modalities for delivery of FVIII and FIX gene therapy to hemophilia patients. However, the future may be in FVIII and FIX gene editing given the promising advantages shown to date with CRISPR/Cas

systems, which include precise chromosomal localization, safe harbour, permanent integration into genome, suitability for all ages (including fetuses), and possibility of repeat dosing to achieve therapeutic levels.

Report from 2nd WFH Gene Therapy Round Table: unfinished business

GLENN PIERCE, MD, PHD, VICE PRESIDENT, MEDICAL, WORLD FEDERATION OF HEMOPHILIA

The WFH Gene Therapy Round Table (GTRT) brings together a diversity of stakeholders with gene therapy expertise, with about 80 representatives from over 20 countries including patients, payers, health technology assessment experts, physicians, nurses, regulators, and manufacturers.

The first GTRT in 2018 focused on the expected challenges and opportunities that gene therapies for hemophilia will bring to the hemophilia community. Six challenges were identified: the need for standardized efficacy endpoints with regulator consensus; known and unknown long-term safety concerns; global access to gene therapy; paradigm shifts in treatment goals and in organization and delivery of care for people with hemophilia; preservation of solidarity and security of the local and global hemophilia community; and expansion of the indication from the "ideal" patients enrolled in phase 3 trials to those who were not included, i.e., pediatric patients.

The second GTRT in April 2019 produced consensus statements on four challenges identified at the first GTRT, summarized below.

- The evolution of gene therapy must be underpinned by a solid scientific and ethical research framework and its success of gene therapy is critically dependent on partnership with a patient-centred approach involving collaboration between all stakeholders—academics and healthcare providers, people with hemophilia and national member organizations, governments, payers, nongovernmental organizations, industry, and regulators—to bridge the gap to access globally.
- Every person with hemophilia who is exposed to a gene therapy product for hemophilia should be followed for safety outcomes and duration of efficacy in a registry over their lifetime. Important safety and efficacy outcomes to collect are mortality, co-morbidities, factor level, and bleeding events.
- All groups, except those with known safety concerns (e.g., active liver disease) should eventually have access to gene therapy.
- For hemophilia A and B, the ideal range of factor expression is 50% to 100%; this is steady-state expression as measured by the best available assay that reflects clinical hemostasis.

The third GTRT to be held in 2020 will continue to explore issues around bringing gene therapy to the hemophilia community.

Target levels post-therapy in the context of joint health

JOHANNES OLDENBURG, MD, HAEMOPHILIA CENTRE, UNIVERSITY CLINIC, BONN, GERMANY

It is important to understand the factor activity and trough levels needed in specific clinical conditions to prevent joint disease, said Dr. Johannes Oldenburg. Numerous studies have established the role of primary prophylaxis in prevention of joint damage, and that initiation of primary prophylaxis at an earlier age improves long-term outcomes. However, recent studies show joint arthropathy in patients on early lifelong prophylaxis at 30-40 years of age, particularly in the knee and elbow joints. Studies also show better outcomes and significantly less spontaneous joint bleeds

with 3-5% factor trough levels than below, but above 5% trough levels are needed to almost eliminate spontaneous joint bleeds. Therefore, current standard prophylaxis regimens delay or reduce subsequent joint damage but do not eliminate joint bleeding and subsequent joint damage that develops over decades. The European Directorate for the Quality of Medicines (EDQM) has recommended trough levels above 3.25% and is working to establish consensus in Europe.

Joint disease is found in patients with moderate or mild hemophilia, and more prevalent in carriers with factor levels below 40% compared to their counterparts of similar age in the general population. Carriers with factor levels above 40% show no difference in joint disease compared to their counterparts in the general population. Clinical observations indicate that 5-10% factor trough levels may be needed to prevent joint arthropathy and 10-20% levels may be needed to prevent chronic synovitis. Some patients on emicizumab, which provides 10-20% factor activity levels, have developed chronic synovitis, indicating that this range is insufficient to prevent spontaneous bleeds. Higher trough levels are need to the lower the risk of spontaneous and microbleeds. Factor activity and trough levels of 30-50% are needed to achieve full protection to maintain joint health —this should be the minimum target for gene therapy, Dr. Oldenburg said. Current therapies would need to be used off label at higher frequency to achieve such trough levels.

Overview of gene editing prospects for hemophilia

HAIYAN JIANG, PHD, GENECEPTION THERAPEUTICS, SHANGHAI, CHINA

Dr. Haiyan Jiang gave an overview of current endeavours in gene editing for hemophilia gene therapy and issues that need to be resolved to make gene editing a reality. Various platforms for gene therapy using AAV and lentiviral vectors for FVIII and FIX gene transfer are the most advanced in clinical development and have demonstrated clinical cure based on endpoints such as ABR and factor usage. However, AAV-based gene therapies have several limitations. Long-term efficacy and safety are yet to be determined and high prevalence of pre-existing anti-AAV antibodies limit access to a subset of the population. In addition, AAV is short-lived and not sustainable in pediatric patients; and has unfavourable risk/benefit for hematopoietic stem cell transplantation (HSCT), and low efficiency of gene correction/insertion by gene editing in quiescent HSC. Furthermore, there are manufacturing challenges and the high cost of gene therapies is prohibitive for developing countries. These issues can be addressed by gene editing, which may offer applicability to all patients; more persistent and durable efficacy; and more precise and safer editing allowing possible treatment of infants.

The true advantage of gene editing is to benefit the pediatric population, which is not amenable to AAV-based gene therapy. Zinc finger nuclease (ZFN) and CRISPER gene editing platforms have led to promising results. A 2011 preclinical study using ZFN for *in vivo* targeted gene insertion of FIX intron 1 by AAV8 achieved about 2-3% integration of the expression of FIX antigen in neonatal hemophilia B mice. A 2019 study showed improvement of ZFN technology using CRISPER/Cas9 gene editing and the hyperactive FIX Padua variant to increase FIX activity in addition to the antigen levels; and targeted gene insertion in FIX exon 2 achieved about 10% integration of FIX antigen level and close to normal FIX activity levels. Both approaches have shown long-term sustainability in neonatal animal models with FIX expression sustained for over 30 weeks.

ZFN for targeted FVIII gene insertion at the albumin locus has also produced good results; targeting mAlb intron 1 for b domain deleted FVIII cDNA insertion with two AAV8-ZFN vectors and one AAV8-FVIII donor vector has demonstrated high level expression in adult hemophilia mice. Delivery of LNP encapsulated CRISPER/Cas9 mRNA/sgRNA targeting mAlb intron 1 and AAV8-FVIII cDNA donor flanked by a splice acceptor and PA in adult hemophilia A mice or NSG mice also achieved 30-70%

FVIII levels up to 4 months at a gene integration frequency of 0.5-3%. Repair of double-strand breaks induced by CRISPR/Cas9 leads to large deletions and complex rearrangements. Long-read sequencing and long-range PCR genotyping revealed significant on-target mutagenesis and large deletions over many kbs and complex genomic rearrangements at the targeted sites.

In order to really be applicable to the majority of the population, the field must move away from using viral vectors, Dr. Jiang said. Most studies rely on AAVs for gene transfer but have challenges related to high vector doses, immune responses, limited patient population, and persistent expression of nuclease which are a long-term safety concern. Non-viral vectors (e.g., LNP) so far have been developed to deliver small molecule drugs and antisense oligonucleotides but require development and optimization to deliver large molecules such as mRNA/gRNA, RNP, or ssDNA.

The key development that is needed to make gene editing a cure for hemophilia is the translation from mouse to human at a clinically feasible vector dose. In terms of efficacy, preclinical studies in mouse models have demonstrated near normal to supra-physiological levels of factor expression; few gene insertion events at albumin locus are adequate to drive high level transgene expression; and neonates showed comparable or higher gene insertion efficiency than adults. However, in terms of safety, assessment of genotoxicity and human genome specificity still quite primitive. Deep sequencing of potential off-targets based on in silico prediction is not informative. There is need to extensively characterize small insertions, large deletions, and chromosomal rearrangements using minimally biased and orthogonal methods and karyotyping to assess potential chromosomal translocations in order to understand the biological impacts of those rearrangements and identify the acceptable levels of rearrangements to move forward to clinical trials.

Gene therapy for rare bleeding disorders: what is the regulatory pathway?

ANDREA LASLOP, MD, EUROPEAN MEDICINES AGENCY (EMA)

Dr. Laslop spoke about the European Medicines Agency's overall regulatory approach to gene therapy treatments. Many novel products are under development in hemophilia. This includes gene therapies which have the potential to enable constant endogenous FVIII or FIX expression maintaining factor levels close to or within the normal range, and thereby provide ongoing prevention of low trough levels with reduced risk of bleeding and potentially even phenotypical cure.

There are several important particulars of clinical development of hemophilia gene therapies which in general have been accepted by regulatory bodies:

- open-label, single arm, single-dose studies (intra-patient controlled with a run-in phase of sufficient duration of at least 6-12 months to determine the baseline bleeding rate);
- exploratory and dose-finding phase 1/2 studies in adults;
- confirmatory phase 3 studies in adults and adolescents (intra-patient controlled with a run-in phase of sufficient duration of at least 6-12 months to determine the baseline bleeding rate) of effects on the preferred co-primary endpoints (factor activity levels and ABR over 52 weeks) and secondary endpoints (external factor consumption, bleeding [number, severity, location], and quality of life);
- long-term follow-up with clinical studies for at least 5 years.

In addition to post-marketing extension studies, observational studies and registries will be needed to capture long-term data of safety and durability of efficacy, i.e., factor expression. Important considerations for registries include data elements, sources, ownership, and analysis of data. Early and comprehensive planning of data generation is crucial.

Clinical development studies in younger age groups are expected to start after adult patient data are available and demonstrate safety and benefits. Manufacturers must submit a Pediatric Investigation Plan (PIP) for approval by the EMA Pediatric Committee that includes definition of patient numbers, age cohorts, and a step-wise approach. Pediatric dosing is more challenging due to dilution effects with growth of the liver and expansion of blood volume throughout the development years until adulthood is reached.

Gene therapies for hemophilia are a promising new treatment approach expected to provide improved outcomes and quality of life but uncertainties about long-term efficacy and safety still exist, Dr. Laslop concluded. Early interaction between all stakeholders is key for successful development, authorization, and patient access.

VON WILLEBRAND DISEASE & WOMEN AND BLEEDING DISORDERS

CHAIR: DAWN ROTELLINI, NATIONAL HEMOPHILIA FOUNDATION, USA

Ms. Dawn Rotellini opened the session with an audience poll on what diagnosis term will most likely help women with bleeding disorders advocate for better treatment and care; 79% voted in favour of hemophilia (mild, moderate, severe) while 21% voted for symptomatic carrier.

VWD Treatment Guidelines: defining priorities

NATHAN CONNELL, MD, BRIGHAM AND WOMEN'S HOSPITAL; HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS, USA

Dr. Nathan Connell gave an overview of an international collaboration to develop new evidence-based clinical practice guidelines for von Willebrand disease. In early 2017, American Society of Hematology (ASH), ISTH, NHF, and WFH convened a working group of clinicians, patients, and patient organization representatives. The working group recommended the development of two individual guidelines on diagnosis and management and developed list of essential topics.

In early 2018, the chairs defined priorities, logistics, and timeline; and the working group agreed on the importance of conducting a needs assessment survey to guide prioritization of the topics identified. The survey was disseminated to the membership of the organizations in June 2018, and publicized on social media and at the WFH Congress and ISTH Scientific and Standardization Committee meeting over the next months. There were 601 respondents to the survey, of whom 51% were patients/caregivers and 49% were healthcare providers. VWD diagnostic criteria/classification and bleeding assessment tools were rated highest, while screening for anemia and iron deficiency was rated lowest. For VWD management, treatment options for women and treatment options for surgical patients were rated highest while plasma-derived therapy vs. recombinant therapy was rated lowest. Statistically significant differences in means were found for specific topics between patients/caregivers and healthcare providers. Recommendations will be developed based on the systematic reviews and evidence search; this will be followed by an open comment period to gather input from other stakeholders. Publication is anticipated mid-late 2020.

Concentrate treatment of VWD

BARBARA KONKLE, MD, UNIVERSITY OF WASHINGTON; BLOODWORKS NORTHWEST. SEATTLE, WASHINGTON, USA

Dr. Barbara Konkle gave an overview of treatment options for preventing or treating bleeding in patients with VWD, which comprise antifibrinolytic therapy, desmopressin, and factor concentrates.

For major surgery or more severe types of VWD, treatment consists of VWF-containing factor concentrates, often in conjunction with antifibrinolytic therapy. For heavy menstrual bleeding, hormonal contraceptives have been the first line therapy but antifibrinolytic therapy plays an important role; other options include intranasal or subcutaneous high concentration desmopressin and VWF-containing concentrates.

A multicentre European study of patients with severe type 1 and type 2 VWD demonstrated FVIII response and VWF ristocetin cofactor response (VWF:RCo) to desmopressin, with variability of response between patients and variation in response rate according to VWD types. Type 1 VWD is usually responsive to desmopressin; type 2 (type 2A, type 2M, 2N) is generally less responsive to desmopressin, with the exception of some specific type 2A gene defects. This reinforces the need to test patients to assess their response to desmopressin prior to clinical use.

Heavy menstrual bleeding is a common and major health problem in women with VWD, resulting in major quality of life issues. A 2019 survey of U.S. hemophilia treatment centres found that over 60% of women with VWD experienced heavy menstrual bleeding; combined oral contraceptives were the most common therapy, followed by tranexamic acid and desmopressin, then VWF which was considered a third line therapy. A literature review found 101 women treated with VWF concentrates, with a wide range in dose (33-100 IU/kg) and frequency (1 to 6 days). A prospective, randomized, crossover study is now underway comparing tranexamic acid to recombinant VWF concentrate as treatment to minimize menorrhagia in women with VWD.

Various studies in women without VWD have demonstrated that VWF levels rise during pregnancy, up to 350% from baseline and return to baseline level after delivery. However, better understanding and management of postpartum hemorrhage in women with VWD and specific guidance for childbirth planning are needed. A prospective multicentre study is underway on the use of VWF in pregnant women with VWD and non-corrector VWF/FVIII levels (<50-100%), with dosing to minimum trough levels of 100–150% for childbirth and postpartum hemorrhage and maintenance of at least 50% VWF activity levels for 5 to 10 days after delivery.

Dr. Konkle also described several studies on prophylaxis in VWD. A study based on retrospective and prospective VWD Prophylaxis Network data from over 100 patients with severe VWD who were desmopressin unresponsive found significantly decreased bleeding in patients on prophylaxis, particularly less epistaxis and GI bleeding, which are the most common reasons for prophylaxis, and less hemarthroses and heavy menstrual bleeding. In addition, a 2019 study based on Swedish registry and VWD Prophylaxis Network data reported that the most common reason for hospitalization was GI bleeding and the most common reason for outpatient visit was heavy menstrual bleeding. Prophylaxis decreased hospitalization by 40%. There remain gaps in data on optimal treatment of VWD with factor replacement therapy, particularly for pregnancy management and heavy menstrual bleeding management; and in surgical procedures, particularly for tonsillectomy and colon polypectomy.

Carriers or symptomatic hemophilia?

ROSELINE D'OIRON, MD, REFERENCE CENTRE FOR HAEMOPHILIA AND CONGENITAL BLEEDING DISORDERS, BICÊTRE HOSPITAL, PARIS, FRANCE

Dr. Roseline d'Oiron gave an overview of current and common understanding of carriers of hemophilia, issues surrounding nomenclature and definitions, and challenges and needs in the management of care. It has been recognized that about one-third of hemophilia carriers have low factor levels below 40% (40 IU/dL) and experience abnormal bleeding, most frequently heavy menstrual bleeding and postpartum hemorrhage.

The Scientific and Standardization Committee of the ISTH has proposed terminology and categorization of hemophilia carriers:

- asymptomatic carrier: FVIII/FIX level >50% (50 IU/dL), no bleeding symptoms
- symptomatic carrier: FVIII/FIX level <50% (50 IU/dL), bleeding symptoms
- mild hemophilia carrier: FVIII/FIX level of 5-50% (5-50 IU/dL)
- moderate hemophilia carrier: FVIII/FIX level of 1-5% (1-5 IU/dL)
- severe hemophilia carrier FVIII/FIX level <1% (<1 IU/dL)

Dr. d'Oiron noted the discrepancy between the threshold for mild hemophilia carriers defined as FVIII/FIX level of 5-50% (5-50 IU/dL) compared to the threshold for males with mild hemophilia defined as FVIII/FIX level of 5-40% (5-40 IU/dL). Other proposals suggest that a symptomatic carrier be defined as FVIII/FIX level ≤ 30% (30 IU/dL), and that carriers with factor levels of 30% or lower in fact have mild hemophilia and must be treated accordingly.

Consequences related to non-recognition of females with hemophilia include: delay in clinical diagnosis and loss of opportunity for treatment of bleeding episodes; delayed diagnosis of infectious complications; delayed genetic diagnosis; denial of insurance coverage; negative emotional and behavioural responses to medical experiences; and exclusion from clinical studies. Challenges include the lack of criteria for diagnosis; lack of recognition of hemophilia treatment centres as a suitable for care; need for multidisciplinary hematology/gynecology clinics; need for inclusion in patient registries/databases and defined inclusion criteria; and need for research.

According to various estimations, females should constitute about 30% of the hemophilia population; and one-third of carriers have low FVIII or FIX levels. However, hemophilia carriers currently make up only 1-12% of hemophilia patients included in national patient registries/databases. Girls and women with hemophilia are likely not rare, as thought in the past; rather, many may be undiagnosed or not included in registries. Challenges include lack of consensus on terminology for females with low FVIII or FIX levels (i.e., female with hemophilia, female with FVIII or FIX deficiency, symptomatic carrier, or asymptomatic carrier) and heterogeneity of definitions used for inclusion in registries. Formalized and standardized vocabulary and inclusion criteria are needed.

There are two key issues in the management of care for carriers and females with hemophilia, risk of genetic transmission and bleeding risk. Genetic testing is performed to determine if a female is a carrier or non-carrier, whereas coagulation tests (i.e., FVIII/FIX activity levels) are performed to determine whether she has hemophilia or not. Genetic diagnosis and bleeding disorder diagnosis are frequently performed at the same time in adulthood (>18 years of age); current literature indicate the median age of carriers is 40 years of age. Ideally, factor assays should be performed in carriers and potential females with hemophilia much earlier in life, before 3 years of age as with males, and genetic testing should be performed when they are determined to have low FVIII/FIX levels; however, some countries prohibit genetic testing before 18 years of age. Dr. d'Oiron highlighted the urgent need for research and data collection. Inclusion in databases is key. Increased outreach and awareness among treaters and unidentified and undiagnosed females are needed.

CLOSING REMARKS

Dr. Pierce thanked the speakers, participants, and sponsors for their engagement in the 2019 WFH Global Forum, and their contributions to the exchange of scientific knowledge and perspectives on important issues and topics related to the treatment of bleeding disorders and global access. The audience was polled again on the questions from the opening session. Regarding the biggest threat to patients today, 70% voted for supply and access to treatment products, while 20% voted for inhibitors. Inhibitors were identified as the biggest safety threat today. In addition, 82% identified price as the biggest supply threat. The audience was divided on when gene therapy will be commercially available to patients, with 31% voting in 1 year, 35% voting for in 3 years, and 35% voting in 5 years.

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APPENDIX: GLOBAL FORUM AUDIENCE POLL RESULTS

1. What do you think is the biggest threat to patients today?

Inhibitors	24%
Supply/access to treatment products	65%
Pathogen transmission	2%
Other	9%

2. What do you think is the biggest SUPPLY threat today?

Price	64%
Regulatory issues	15%
Lack of manufacturing capacity	8%
Other	13%

3. When do you think gene therapy will be commercially available to patients?

One year	30%
Three years	29%
Five years	41%

4. What percentage of severe hemophilia A patients in North America and Europe do you think will have had gene therapy within 5 years of it becoming commercially available?

5%	32%
10%	26%
20%	29%
30%	11%
50%	2%

5. What percentage of severe hemophilia B patients in North America and Europe do you think will have had gene therapy within 5 years of it becoming commercially available?

5%	33%
10%	29%
20%	23%
30%	11%
50%	4%

6. What do you think is the biggest SAFETY threat today?

Inhibitors	46%
vCJD	0%
Viral transmission	4%
Unknown pathogens	23%
Thrombotic events	21%
Other	6%

7. Which of the following most closely represents your viewpoint?

Sustained production of virally inactivated cryoprecipitate should be integrated into routine operations of blood establishments.	9%
Virally inactivated cryoprecipitate should not be regarded as a substitute for Clotting Factor Concentrates (CFCs) but rather used only in the transition to CFCs where resource constraints exist.	49%

I agree with both statements	35%
Neither statement represents my viewpoint	6%

7b. Which of the following most closely represents your viewpoint?

Sustained production of virally inactivated cryoprecipitate should be integrated into routine operations of blood establishments.	5%
Virally inactivated cryoprecipitate should not be regarded as a substitute for Clotting Factor Concentrates (CFCs) but rather used only in the transition to CFCs where resource constraints exist.	35%
I agree with both statements	60%
Neither statement represents my viewpoint	0%

8. In your opinion, what is the value of defining an extended half-life product

The EHL definition will address current confusion as to which products are standard half-life and which are an extended halflife.	43%
The EHL definition will help payors to make reimbursement decisions	14%
The definition of an EHL will help manufacturers to market their products better	4%
The definition of EHL is purely academic curiosity with no other value	10
The EHL definition will help patients with choice of products to use.	30%

8b. In your opinion, what is the value of defining an extended half-life product

The EHL definition will address current confusion as to which products are standard half-life and which are an extended half-life.	65%
The EHL definition will help payors to make reimbursement decisions	7%
The definition of an EHL will help manufacturers to market their products better.	1%
The definition of EHL is purely academic curiosity with no other value	4%
The EHL definition will help patients with choice of products to use.	23%

9. What do you think will be the main safety issue with the novel (non-replacement) therapies?

Bleed control	20%
Thrombosis	55%
Supply of product	11%
Anti-drug antibodies	9%
Allergic reactions	5%

10a. Is a national tender the best way to procure therapy?

Yes	61%
No	39%

10b. Is a national tender the best way to procure therapy?

Yes	76%
No	24%

11. Which of the following is not a social media site?

Tumblr	0%
Tik Tok	14%
Twitter	0%
Pinterest	2%
Glenn's daily news	84%

12. How many tweets are sent daily?

5 million	0%
50 million	11%
500 million	36%
5 billion	34%
50 billion	20%

13. Under what condition(s) will the prevalence of hemophilia equal the prevalence of birth for hemophilia?

All patients are accounted for and counted only once	19%
Treatment is available	0%
Mortality rate of hemophilia is the same as the mortality rate of the population	21%
All of the above	51%
None of the above	10%

14. What diagnosis term will most likely help women with bleeding disorders advocate for better treatment and care?

Symptomatic Carrier	21%
Hemophilia (mild, moderate, severe)	79%

15. What do you think is the biggest THREAT to patients today?

Inhibitors	20%
Supply/access to treatment products	70%
Pathogen transmission	2%
Other	7%

16. What do you think is the biggest SAFETY threat today?

Inhibitors	84%
vCJD	0%
Viral transmission	0%
Unknown pathogens	16%

17. What do you think is the biggest SUPPLY threat today?

Price	82%
Regulatory issues	10%
Lack of manufacturing capacity	2%
Other	6%

18. When do you think gene therapy will be commercially available to patients?

One year	31%
Three years	35%
Five years	35%

19. Did this Global Forum:

Exceed your expectations	53%	
Meet your expectations		47%
Not meet your expectations	0%	

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