THE 10th WFH GLOBAL FORUM

on Research and Treatment Products for Bleeding Disorders

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PROCEEDINGS

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The Proceedings of the World Federation of Hemophilia's Tenth Global Forum on Research and Treatment Products for Bleeding Disorders

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Introduction

The 10th WFH Global Forum on Research and Treatment Products held in Montreal, November 8-10, 2017, brought together 190 international scientists, clinicians, patient representatives, health and regulatory officials, and industry representatives to exchange the latest scientific and clinical research in hemophilia and other inherited bleeding disorders and global perspectives on treatment safety, affordability and availability. This Global Forum clearly marked a major milestone in the treatment of hemophilia, with a number of medical breakthroughs now available that provide superior treatment outcomes, and potentially curative gene therapies in clinical trial that are beginning to transform patients' lives.

Numerous sessions focused on the revolutionary bleeding disorder therapies in the development pipeline or already in some markets, including extended half-life factor products, gene transfer therapies, and novel bypassing agents. In addition to research, scientific evidence and outcomes, particular attention was given to the uncharted challenges presented by these breakthrough therapies, such as how to minimize safety risks during clinical trials; define core outcomes and trough levels with extended half-life factor products; define efficacy in gene therapy trials; and bridge the gap between state-of-the-art science and the realities of healthcare system fiscal constraints so that patients have access to the best medicines.

The Global Forum also focused on the persistent issues of inadequate access to treatment in developing countries, pathogen safety risk surveillance vis-à-vis plasma-derived products, and inhibitor complications; and recent advances in these areas through intensified international humanitarian aid initiatives, new technologies, and collaboration on inhibitor surveillance and research.

New treatments

The past five years has seen intense development of novel technologies, bypassing agents and gene therapy for hemophilia. As they move through clinical trials towards market authorization, it is essential to approach these novel types of medicines with absolute caution and thoroughly examine all safety aspects in order to ensure utmost safety and protection of patients. A key aspiration of hemophilia treatment is to allow patients to participate in normal activities and enjoy normal lives. Novel and gene therapies in hemophilia hold a lot of promise for reducing some of the burdens of prophylaxis using standard factor concentrates.

Extended half-life factor products

Extended half-life factor products have several potential advantages over standard factor concentrates, including the potential for lower infusion frequency and reduced factor use. There is also optimism extended half-life factor products could improve inhibitor prevention and eradication in hemophilia due to lower immunogenicity. This session presented outcomes from patients in Canada and the United States treated with novel recombinant Fc fusion proteins. Overall, among adult and pediatric patients in Canada, there have been significant decreases in infusion frequency (once weekly prophylaxis in some cases), increased patient adherence to prescribed regimens, and significant decreases in factor use. There were similar results in the US experience, where extended half-life factor concentrates have also been successful in immune tolerance induction.

As extended half-life factor therapies move into the clinical realm, more focus is needed on the outcomes most important to patients including quality of life and participation in physical and sport activities. A two-year, multi-centre study is now underway in Canada to observe outcomes beyond the typical clinical trial outcomes that have been measured in the past, with specific attention to patient-relevant outcomes such as functional status, wellbeing and satisfaction with care, as well as direct medical costs and days

lost from work or school. In addition, an international working group is working to establish consensus on a core set of outcome measures for use in hemophilia clinical care or studies evaluating treatment.

Factor activity and trough levels

Prophylaxis with factor concentrates is based on the concept of achieving a minimum trough of 1% factor VIII (FVIII) and factor IX (FIX) activity levels in order to prevent spontaneous bleeds, with the primary endpoint being annualized bleeding rate. However, the evidence clearly shows that a trough of 1% is inadequate to fully prevent bleeding that leads to joint damage. This session focused on the need for a paradigm shift aiming for a higher trough level and standard of care, given that normal FVIII/FIX activity is 50–150% and that the arrival of novel therapies for hemophilia now makes it possible to aim for factor levels that provide better bleed protection and more closely mimic a normal state in the absence of hemophilia. Aiming for a 15% trough would provide a level of protection that allows people with hemophilia to have normal aspirations and fully pursue opportunities in life. With gene therapy, it is possible to attain sustained 10-30% factor activity levels, which allow for much more unhindered activities as there are no peak or trough levels, while annualized bleed rates are reduced to near zero. There are also no infusion and adherence issues.

Gene therapy for hemophilia

Gene therapy for hemophilia A and B appears to be within a few years' reach and will potentially deliver a cure in the near future. Sustained FVIII and FIX levels above 10% have been achieved in clinical trials, with annualized bleeding rate dependent on joint status at the start of gene therapy and health-related quality of life dependent on joint status and socio-economic circumstances. Gene therapy will allow patients with hemophilia to aspire to and attain much better health outcomes and quality of life; this needs to be taken into account in defining the primary endpoints for clinical trials and clinical practice. Hemophilia gene therapies will require continual research and long-term follow-up beyond clinical development and initiation of therapy. Education is critical and it is essential for patients, clinicians and healthcare providers to get informed and understand the issues as gene therapies move through clinical trial towards market approval.

Affordability of new treatments

The imminent arrival on the market of hemophilia gene therapy with the potential for lifelong curative effects from a single treatment dose raises unique challenges in terms of how to assess their clinical value, estimate the long-term cost offsets, and establish what is fair pricing given limited clinical data and uncertainty on durability of effects. As payers and health technology assessment agencies demand more data and evidence on therapeutic effectiveness, it is crucial for all stakeholders in the hemophilia community to help define the value and core outcomes of the novel and gene therapies for hemophilia in order to make the case for coverage and reimbursement and ensure that patients everywhere have access to the novel therapies entering the market.

Current healthcare systems are largely not set up to accommodate the market entry of many high-cost gene therapies for different diseases anticipated over the next decade, and their profound implications on health outcomes and budget impacts. With hemophilia gene therapy, key challenges to gaining market access are price and uncertainty of long-term safety and sustained effectiveness in the real world. Risk-sharing arrangements and technology leasing reimbursement strategies are ways to resolve such issues so that high-cost breakthrough therapies and genetic cures are affordable to payers and accessible to patients. Gene therapy manufacturers, payers, patients, and policymakers need to work together to resolve these barriers to access and affordability; new pricing and pay-for-performance and annuity payment mechanisms may be needed.

Humanitarian aid initiatives

In 2015, the WFH launched its expanded Humanitarian Aid Program with the goal of securing sustained levels of product donations and greater predictability of donation quantities and timeframes, in order to allow WFH to expand the magnitude and scope of its humanitarian aid in the developing world. Over the past two years, there has been an upsurge in product donations, with major beneficial impacts on access and treatment options for patients in the developing world. In the past, due to limited and fluctuating amounts of product donations, humanitarian aid products were stipulated for use only in two cases, acute bleeds and life-threatening surgeries. Now that larger quantities are available, donated factor products are also being used for preventive surgeries, prophylaxis, and immune tolerance induction.

Access to affordable treatment products

The European Haemophilia Consortium has launched a new program called Partners, with the goal of helping countries with very low factor usage access better factor concentrate prices in order to increase the availability of treatment and per capita use. The Partners Program aims to help countries with low factor usage improve their tender processes to gain access to factor concentrates at significantly lower prices, increase procurement quantities, and increase per capita factor consumption— towards achieving the European Directorate for the Quality of Medicines and Healthcare's recommendations of at least 4 IU factor VIII per capita for hemophilia A and 0.5 IU factor IX per capita for hemophilia B.

Better understanding of the features and dynamics of factor pricing could help improve access to treatment. Careful analysis is needed when comparing price and cost of novel agents to standard therapies, taking into account the impacts of infusion frequency and dosing. Biosimilars, i.e., generic versions of off-patent biological drugs, present an opportunity to improve access to affordable care. Data from the European Union show the introduction of biosimilars has resulted in substantial drops in price for many drugs. Yet while a number of biosimilar factor concentrates have been introduced, mostly in markets in developing countries, there have not been similar drops in price. Development of biosimilar recombinant factor underway in Russia may bring about the price reductions and increased availability hoped for towards being able to achieve global access.

Inhibitors to factor treatment

Inhibitor development is one of the most serious and difficult complications of hemophilia treatment. Clinical management of inhibitors involves treatment or prevention of bleeding with the use of hemostatic bypassing agents, and immune tolerance induction therapy. Experts from Canada, the United States and Germany presented the latest research on inhibitors, including ongoing investigation of the differences in inhibitor risk among recombinant factor products and plasma-derived factor products. Key priorities to improve inhibitor prevention and management include: advance national inhibitor surveillance and clinical research; optimize laboratory assays and improve laboratory monitoring and scientific understanding of the early stages of immunogenicity; define a core data set and parameters to enable harmonized data collection and exchange; and advance investigation of new agents and alternative hemostatic therapies and gene therapies in terms of their potential to provide better efficacy for patients with inhibitors.

World Bleeding Disorders Registry

The WFH World Bleeding Disorders Registry rolled out at the end of 2017 is expected to facilitate clinical data collection and research, as well as national and international research collaboration and data exchange. Furthermore, it will help demonstrate the tangible impacts of the WFH Global Alliance for Progress and Humanitarian Aid Programs for people with bleeding disorders in developing countries receiving donated products from the WFH. Global involvement of treatment centres, national member organizations, and patients is vital to the registry's objectives and success.

WELCOMING REMARKS

ALAIN WEILL, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA (WFH)

WFH President Alain Weill welcomed 190 attendees from 34 countries to the World Federation of Hemophilia's 10th Global Forum on Research and Treatment Products, in Montreal, November 8-10, 2017. He noted how far treatment has advanced in the 17 years since the first WFH Global Forum in 2000, which focused on blood safety and supply risks, production issues and resulting recombinant factor concentrate shortages, and other challenges related to resource utilization and cost economics. This 10th WFH Global Forum would present revolutionary bleeding disorder therapies in the development pipeline or already on the market, including extended half-life factor products, gene transfer therapies, and novel bypassing agents; while also focusing on persistent issues such as inadequate access to treatment in developing countries and the ongoing clinical challenge of inhibitors, and recent advances in these areas through international humanitarian aid initiatives and collaboration on inhibitor surveillance and research. It is imperative to ensure that patients everywhere have access to safe and effective treatment, including the novel therapies entering the market, Mr. Weill said. He thanked industry partners who provided vital financial support for Global Forum 2017 and wished participants fruitful discussions towards solving these issues.

Throughout the Global Forum, participants were polled on a series of questions to gauge their views on supply, safety and access issues in bleeding disorders treatment today. (See Appendix: Global Forum Audience Poll Results.)

INHIBITORS – SOLVING THE PROBLEM

CHAIR: MARIJKE VAN DEN BERG, VICE PRESIDENT MEDICAL, WORLD FEDERATION OF HEMOPHILIA

The formation of inhibitors (inhibitory antibodies against infused factor concentrates) is among the most serious complications in hemophilia treatment. The European Medicines Agency's (EMA) current revision of its guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products, with public consultation just underway, provided a very timely and pertinent context for discussion.

Inhibitors – Defining the problem

DAVID LILLICRAP, MD, PATHOLOGY AND MOLECULAR MEDICINE DEPT., QUEEN'S UNIVERSITY, KINGSTON, ONTARIO, CANADA

Dr. David Lillicrap gave an overview of the epidemiology and management of inhibitors, with some perspectives about inhibitor testing, risk factors and costs, and priorities for advancing treatment. About 30% of previously untreated patients (PUPs) with severe hemophilia A develop inhibitors to factor VIII (FVIII) after a median of 10-20 exposure days. The incidence of factor IX (FIX) inhibitors is much lower, occurring in about 4% of PUPs with severe hemophilia B; however, FIX inhibitors are sometimes associated with severe allergic symptoms and therefore can be particularly challenging. There are two components to the clinical management to inhibitors: treatment or prevention of bleeding with the use of hemostatic bypassing agents; and immune tolerance induction (ITI) therapy, which is successful in about 70% of FVIII inhibitor cases but is infrequently successful for FIX inhibitors.

Laboratory inhibitory testing is a key challenge. The Bethesda assay is the standard test used to measure factor inhibitor level, which is referred to as inhibitor titer and quantified in Bethesda units (BU). However, results from the WFH External Quality Assurance program over the years show significant variations in assay results, which have been attributed in part to differences in application of methodology. There are ongoing efforts to improve standardization of factor inhibitor assays led by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH). Other types of assays based on detecting non-neutralizing antibodies are being investigated. Recent studies on early anti-FVIII immune response have found IgG1 and IgG4 subclass antibodies with high FVIII affinity in hemophilia A inhibitor patients, which can be detected long before the emergence of the inhibitor response measurable using the Bethesda assay.

There are both genetic and environmental risk factors that influence inhibitor development. A 2010 FVIII genotype study showed F8 gene mutations with multi-domain large deletions are associated with a 70-80% risk of inhibitor development, whereas F8 mutations with intron 22 inversions or single-domain large deletions have 20-25% risk, and F8 mutations with small deletions are low risk. The Hemophilia Inhibitor Genetics Study Combined Cohort study has identified at least 53 single nucleotide variants that regulate the immune response and are predictive of inhibitor status. Genotype and immunogenotypic data could be used to identify untreated patients at greater or lesser inhibitor risk and allow preventive intervention and predictive management of care.

A recurring issue is whether recombinant factor products carry a higher inhibitor risk than plasma-derived factor products. The RODIN study evaluated data from 574 severe hemophilia A PUPs followed for up to 75 exposure days. It found similar inhibitor risk and incidence with plasma-derived and recombinant products; and a 1.6-fold increased inhibitor risk with second-generation full-length recombinant products compared to third-generation full-length recombinant products. However, the 2016 SIPPET study on incidence of FVIII inhibitors in PUPs with severe hemophilia A found strong evidence of an increased risk with recombinant FVIII compared to plasma-derived FVIII products. The prospective randomized

trial involving 251 hemophilia A patients found an incidence of 44.5% with recombinant products and 26.8% with plasma-derived products. The 2017 FranceCoag Cohort study of 144 PUPs treated with a plasma-derived FVIII product and 385 PUPs treated with one of two recombinant FVIII products found significantly different inhibitor incidence rates of 22.5% for the plasma-derived product, and 31.6% and 50.1% with the full-length recombinant products.

Inhibitor development is a difficult and expensive complication. A 2015 study cited US data reporting median annual drug cost of US$47,626 (EUR 42,459) for patients without inhibitors, and US$191,301 (EUR 170,545) for patients with inhibitors.

Priorities towards advancing inhibitor prevention and management of patients with inhibitors include:

- Improve laboratory monitoring of the FVIII immune response, especially during the early exposures to FVIII (first 20-30 infusions).
- Improve knowledge of early events in FVIII immunogenicity.
- Advance investigation into the potential of new agents and alternative hemostatic therapies (e.g., emicizumab, hemostasis rebalancing strategies, and gene therapy) to improve therapeutic efficacy and quality of life for patients with inhibitors.

Call to action: Coordinated prevention in PUPs and intervention in patients with inhibitors

STEVEN PIPE, MD, UNIVERSITY OF MICHIGAN, USA

While the incidence of inhibitor development in severe hemophilia A patients is generally estimated to be about 30%, some studies have reported higher rates and inhibitor rates have gradually increased over the last 20 years. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) formed the Inhibitor Prevention and Eradication Working Group in October 2016, to advance two key priorities: ongoing national inhibitor surveillance in order to understand its scope in the United States and obtain benchmarks for strategies to improve surveillance and clinical research; and development of a national scientific agenda for better inhibitor prevention and eradication, including pursuit of research within previously untreated patient cohorts. Specific aims are to help advance strategies to increase enrollment in the national inhibitor surveillance program; support optimization of laboratory assays and monitoring on a national scale; and coordinate a stakeholders committee to prioritize the implementation of interventions to reduce inhibitor development and more effectively eradicate inhibitors.

The working group's primary task is to be a catalyst for the development and implementation of a national agenda for better inhibitor prevention and eradication. Its work is expected to lead to a progressive reduction in the rate and burden of inhibitors within the U.S. hemophilia population, to be documented through the ongoing surveillance infrastructure. Key aims are to help advance strategies to increase enrollment in the national inhibitor surveillance program; optimization of laboratory assays and monitoring on a national scale; development of a coordinated scientific agenda; and development of a review committee of key stakeholders to prioritize implementation of interventions to reduce inhibitor development and more effectively eradicate inhibitors.

MASAC is working with the Centers for Disease Control (CDC), American Thrombosis and Hemostasis Network (ATHN) and the U.S. Hemophilia Treatment Center Network to advance the Community Counts Registry for Bleeding Disorders, and prioritize the need for real-time PUPs data collection harmonized with international studies. The ATHN database includes more than 30,000 patients, with 10,000 patients enrolled in the Registry for Bleeding Disorders. The PUPs Matter real-time surveillance feasibility cohort study has sequenced 10,000 genotypes from a small number of centres in the United States to date; it will

be launched in 2018. The NHF is also collaborating with the CDC, Health Resources and Service Administration, National Hemophilia Program Coordinating Center, and HTCs on standards of care and outcomes, and the HIPS and INHIBIT investigator-initiated research studies. There is a need to address inhibitors in phase 1 consortia/industry trials and phase 2/3 cooperative group/industry trials, as has been done in the U.S. with other high-risk diseases.

Comparison of hemophilia A PUPs data from historic clinical studies and the PedNet registry

CHRISTINE KEIPERT, DEPARTMENT OF HEMATOLOGY AND TRANSFUSION MEDICINE, PAUL EHRLICH INSTITUTE, GERMANY

Christine Keipert described a retrospective comparative study of over 20 years of data from clinical PUPs studies and 16 years of data from the European PedNet Registry, to determine their performance in terms of meeting the EMA FVIII guideline requirements for clinical trials and PUPs. The study compared pediatric clinical trial data from 369 previously untreated and minimally treated patients from 1987-2009 to data collected in the PedNet Registry from 632 severe PUPs from 2000 to 2016.

The existing FVIII guideline came into effect in 2012 and sets out safety and immunogenicity data requirements for clinical trials in PUPs and applications for marketing authorization, including inhibitor testing parameters:

- inhibitor testing before first exposure
- inhibitor testing at 10-15 exposure days
- inhibitor testing at 50 exposure days
- inhibitor testing if there is suspicion of inhibitor development
- confirmation measure of a positive inhibitor test result by a central laboratory
- inhibitor titer measured in BU using the Nijmegen modification
- ≥ 0.6 BU = low titer; > 5 BU = high titer

All the clinical trials reviewed in this study took place before the 2012 FVIII guideline came into effect, therefore, these inhibitor testing parameters were fulfilled to varying degrees depending on when the trials were performed. Most clinical trials in the 1980s and early 1990s gathered safety data but inhibitor testing was only started after 12 weeks of exposure, and without the Nijmegen modification introduced in 1995. The PedNet Registry did collect all inhibitor data of all the newly diagnosed PUPs from the first positive sample and all consecutive samples. Both sources collected clinical efficacy data such as FVIII consumption and treatment response. The FVIII guideline requires follow-up of at least 50 PUPs for at least 50 exposure days; only about half of the clinical trials fulfilled this data requirement, while PedNet collected data from all PUPs for 75 exposure days.

The study also compared clinical trial and PedNet data on cumulative incidence of FVIII inhibitors according to number of exposure days; it found slightly earlier inhibitor detection in the clinical trials, and PedNet diagnosed more high-titer inhibitors due to longer follow-up.

Overall, the study found the data collection in pediatric clinical trials and PedNet to be comparable and able to fulfill the clinical data requirements of the FVIII guideline, and that a robust and well-managed patient registry is as good at detecting inhibitor development as clinical trials. Moving forward, a PUPs data set with core parameters is needed to enable harmonized data collection and exchange. The ISTH published a minimum dataset at the beginning of 2017 while the WFH has its own registry dataset. Now is the time for stakeholders to come together and agree on a core data set and parameters for PUPs data collection, and rules on data sharing. The study has been published in *Haemophilia* and is available online.

Discussion

In the face of uncertainty surrounding serious safety risks such as inhibitors, patients deserve the highest level of protection and the precautionary principle should be applied, said Albert Farrugia of Kedrion. PUPs should be followed in randomized clinical trial prior to marketing authorization and in post-marketing investigation and patient registries to collect data on inhibitor incidence. He also suggested that PUPs should first be exposed to plasma-derived products before recombinant products. Dr. Steven Pipe said in the United States, some clinicians have made the decision to expose PUPs to VWF-containing products but are not collecting data on this—it is a disservice not to collect the data and report on the outcomes.

Dr. Alok Srivastava said the scientific basis upon which the EMA made its decision regarding there being no evidence of difference in risk of inhibitor development between plasma-derived versus recombinant factor concentrates is not widely available. Dr. Marijke van den Berg said a request has been submitted to the EMA Pharmacovigilance Risk Assessment Committee (PRAC) on behalf of the UKHCDO, FranceCoag and PedNet for this data to published and available in the open domain for the community to analyse and refute. Dr. David Lillicrap noted the inexplicable delay to publish the French study, a very high-quality investigation supported by rigorous data collection.

Inhibitor tests are less than robust and much work is still to be done to understand inhibitors and establish reliable assays for detecting inhibitors—the consequences of pathology and phenotype need to be part of the analysis, Dr. Kenneth Mann said.

EXTENDED HALF-LIFE PRODUCTS – DATA ON OUTCOMES: WHAT'S THE EVIDENCE?

CHAIR: DAVID PAGE, WFH COAGULATION PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE CHAIR

Switching to EHL products in children: The Canadian experience

MANUEL CARCAO, MD, CO-DIRECTOR, PEDIATRIC CARE HEMOPHILIA PROGRAM, HOSPITAL FOR SICK CHILDREN, TORONTO, CANADA

Dr. Manuel Carcao described the introduction of two extended half-life (EHL) factor products in Canada. The recombinant FIX Fc fusion protein (rFIXFc) called Alprolix and recombinant FVIII Fc fusion protein (rFVIIIFc) called Eloctate were licensed in Canada in 2014 and made available to patients in 2016 through Canadian Blood Services and Héma-Quebec. Around the same time, due to Canadian Blood Services tender results, Advate was to be phased out and CBS requested that HTCs preferentially switch Advate patients to Xyntha, which was awarded the majority of the recombinant FVIII market share. Patients on other standard half-life products were not forced to switch their treatment.

The results of these initial switches were published in *Haemophilia* in July 2017. From March to October 2016, 139 Canadian patients (43 adults, 96 children) switched to EHL factor products; 109 hemophilia A patients switched to Eloctate and 30 hemophilia B patients switched to Alprolix. While a majority of patients at the Hospital for Sick Children switched to EHL factor—accounting for 54% of all Canadian children who switched—only 15 of 26 HTCs in Canada switched patients in the initial period.

Among patients on Kogenate FS (the other standard half-life FVIII available in Canada at the time), only 30% switched to EHL FVIII; 70% stayed on Kogenate FS (later replaced by follow-on therapy Kovaltry). These preliminary results suggest that when switching was not mandatory most patients/parents were reluctant to switch; the perceived risk of switching possibly outweighed the perceived benefits. Advate patients who had to switch were informed of the merits of the available FVIII products (standard half-life Kogenate/Kovaltry, Nuwiq, and Xyntha; extended half-life Eloctate); 96% chose to switch to EHL FVIII and only 4% opted for another standard half-life product. This suggests that when forced to switch, and given free choice, patients/parents switch to the product that they perceive to be best for the patient.

At the Hospital for Sick Children, 66 patients switched to prophylaxis with rFVIIIFc. Most patients were able to reduce infusion frequency, on average by 1 infusion per week, i.e., a decrease of 52 infusions per patient per year. Average FVIII use decreased by about 15%, from 103 IU/kg/week before the switch to 88 IU/kg/week post-switch. However, 7 patients increased use by significant amounts; this was largely due to the fact that children need to have their doses adjusted upwards to correspond to their growing weight, although some cases involved dose escalation of prophylaxis for patients with frequent bleeds on standard factor concentrates. While formal pharmacokinetic studies have not been done, FVIII levels were measured at different time points. As with standard half-life factor, there was a dramatic range among individual patients. Mean FVIII level was 13% at 48 hours, 4.1% at 72 hours, and 1.8% at 96 hours. The estimated average FVIII half-life was 16-17 hours. In addition, 9 hemophilia B patients opted to switch to prophylaxis with rFIXFc, which resulted in a 40% decrease in FIX use, on average 1.5 less infusions per week. Average FIX use fell from 96 IU/kg/week to 58 IU/kg/week. Most patients opted for less frequent infusion rather than higher trough level; most patients maintained 2-4% FIX levels at all times.

Clinical observations indicate that patients on EHL factor have less spontaneous bleeding, but formal quantification of bleed rates needs to be done. Formal quality of life (QOL) assessment using the hemophilia-specific Cho-Klat questionnaire indicate that overall, many patients experienced improvement in QOL.

Switching to EHL products in adults: the Canadian experience

SHANNON JACKSON, MD, MEDICAL DIRECTOR, BC HEMOPHILIA PROGRAM – ADULT DIVISION, VANCOUVER, BRITISH COLUMBIA, CANADA

Outcome measurement is a fundamental aspect of clinical trials, necessary to establish efficacy and optimum treatment regimens, and in the clinical realm and real world, necessary to optimize treatment and individual care. Dr. Shannon Jackson gave an overview of the transition to extended half-life products in Canada, and outcomes so far in adult patients who switched to rFVIIIFc or rFIXFc, in terms of adherence, bleeds, factor use, pharmacokinetics, and bleed frequency.

Héma-Québec evaluated the EHL products earlier than Canadian Blood Services, and set very restrictive eligibility criteria:

- patients with intravenous access issues who required central line to receive treatment;
- patients who had undergone a pharmacokinetic study and documented short half-life;
- patients given special approval by Ministry.

Canadian Blood Services proposed the same criteria and expanded criteria to include:

- patients already on prophylaxis with standard factor to switch to EHL in order to improve compliance, improve quality of life, or decrease breakthrough bleeding;
- patients on on-demand treatment with standard factor to switch in order to decrease frequent bleeds/bleeding rate.

The Association of Hemophilia Clinic Directors of Canada (AHCDC) collected data from 15 clinics in 8 provinces on early experiences switching to EHL products. From February to October 2016, 139 patients switched to EHL factor products; only 2 of 81 patients in Quebec switched. About 95% of patients were already on prophylaxis and 70% were pediatric patients. About 76% were severe hemophilia A patients and 3% had moderate hemophilia A, while 17% severe hemophilia B patients and 4% moderate hemophilia B patients switched. Switches were made for a variety of reasons: improve quality of life (70%); improve compliance (16%); and decrease bleeds on prophylaxis (8%). Factor utilization data showed a 19% median decrease in factor use among severe hemophilia A patients and a 50% median decrease among severe hemophilia B patients, and decreases in number of infusions per patient per week.

Dr. Jackson described the outcomes to date from 9 adult patients with severe hemophilia A at her clinic in British Columbia who switched to EHL therapy with rFVIIIFc. Seven patients were on prophylaxis at the time of the switch; patients had a median age of 52 (age range 34-65 years) and a fair amount of arthropathy. Patients were followed over a median 8 months of exposure (range 2-16 months). Overall, there was a decrease by 1 infusion per week per patient, similar to the pediatric group. The median joint bleeding rate remained the same. Formal assessment of patient adherence to their prescribed infusion regimen found an increase from 68% pre-switch to 85%. Overall, factor use decreased by about 10 IU/kg/week, from 73 IU/kg/week to 63 IU/kg/week.

In addition, five adult severe hemophilia B patients switched to EHL therapy with rFIXFc. Patients had a median age of 35 (age range 20-57). All were on prophylaxis, with a mean of 3 infusions per week (range 1-7). Patients were followed over a median 19 months of exposure. Almost all but 1 patient went on once weekly treatment with rFIXFc; one patient who had previously been on almost daily treatment went on twice weekly therapy. There was no change in median joint bleeding rate. Treatment adherence increased from a median of 73% to 86% adherence, while median factor use decreased from 79 IU/kg/week to 56 IU/kg/week.

A two-year, multi-centre study is now underway in Canada to observe outcomes beyond the typical clinical trial outcomes that have been measured in the past. The Study of Observation Outcomes in Hemophilia with Extended and Standard Half-Life Factor (SOOTHES) is enrolling both patients with moderate/severe hemophilia A or B who switch to EHL factor products and those who remain on standard factor concentrates.

Switching to EHL products in the United States

STEVEN PIPE, MD, UNIVERSITY OF MICHIGAN, UNITED STATES

Dr. Steven Pipe described the US experience switching to extended half-life factor products. There is some optimism that EHL factor products could improve inhibitor prevention and eradication in hemophilia. EHL factor molecules may have low immunogenicity, based on the mechanisms of action; however, data needs to be collected formally. Inhibitor eradication may be higher with EHL products, as there is biological rationale for improved immunomodulatory impact with Fc fusion proteins and anecdotal evidence of improved immune tolerance induction with rFVIIIFc. It is essential to document and delineate the improved outcomes achievable with EHL factor products in order to justify the price.

Early switches to EHL factor were primarily driven by the medical need for effective treatment for hemophilia patients with stubborn breakthrough bleeding and unresolved target joints despite aggressive prophylaxis. The switches have been universally satisfactory; there has particularly been high satisfaction with alternative dosing regimens that generally do not appear on the product labeling. Dosing every 72 hours has been a fairly popular regimen; adherence does not seem to be difficult, with the use of mobile devices for reminders. A less frequent dosing regimen of every 3.5 days has liberated many families compared to the standard dosing regimens. Some patients were initiated at the same dose and interval as their standard therapy, demonstrated good efficacy, then obtained trough levels at extended intervals (48, 72 and 96 hours); the interval was then stretched if appropriate. Abbreviated sampling is being used to estimate half-life benefit, rather than full PK analysis. Breakthrough bleeds are managed using the EHL factor agents.

Dr. Pipe described five cases at his centre in which switching to EHL factor has improved patient outcomes in terms of treatment adherence, resolution of target joint bleeding, pharmacokinetic tailoring for higher factor and trough levels, immune tolerance induction, and reduced frequency and burden of prophylaxis. In one case, a young patient on continuous ITI for almost five years was switched to rFVIIIFc; inhibitor titer declined within a few weeks of initiation of rFVIIIFc, reaching a negative inhibitor titer six months later. There are now two prospective studies using rFVIIFc in ITI to try to collect this data formally**.**

A study of prophylaxis with EHL factor found the majority of hemophilia B patients dosing with rFIXFc at once weekly intervals, and some dosing at shorter intervals, while some have stretched their dosing interval to 10 days or even 2 weeks; similar variability was seen across all the age groups. With rFVIIIFc, the greater variability in half-life among hemophilia A patients was evident in the bigger range of dosing regimens, with the majority of patients on a twice weekly dosing regimen. In both hemophilia A and B, adult and pediatric patients who switched to EHL factor have demonstrated increased adherence in the home-based therapy. It is important to note that pharmacokinetic tailoring and individualized prophylaxis were built into the rFVIIIFc clinical trials, given the great variability of FVIII half-life. Many patients who switched from standard FVIII to rFVIIIFc were able to shift to dosing at longer intervals while some did not change dosing intervals.

In the phase 3 clinical trials of rFVIIIFc (called A-LONG and ASPIRE), most adult and pediatric patients maintained or increased physical activity levels; annualized bleeding rates (ABR) remained low with

therapy at a similar average weekly dose. Patients showed improved joint health scores in years 1 and 2 of ASPIRE and continued improvement over the course of follow-up, with benefits seen in target joints and severe arthropathy, most notably in the areas of swelling, range of motion, and strength.

A recent US study of insurance costs showed the cost impacts of EHL products. Among 21 patients who switched to EHL factor, 14 of 16 of FVIII patients and 4 of 5 FIX patients reduced infusion frequency and extended dosing intervals. In terms of average annualized cost per patient, 75-80% of patients experienced incremental costs with EHL factor compared to standard factor. The cost of standard FVIII was $0.97-2.06/IU, while EHL FVIII cost $1.19-2.56/IU, representing an overall 67% increase. The cost of standard FIX was $0.81-1.41/IU, while EHL FIX cost $2.21-4.11/IU, representing an overall 173% increase. However, the better outcomes and value to patients must be factored into the equation—all patients are doing much better on the EHL factor products. Although many of the EHL therapies come at significant increases in cost, there is medical justification for their use and it is important to ensure that patients have access to these products.

Discussion

During clinical trials, there were no cases of inhibitors to the EHL products; to date, this has carried out in patients receiving the product in the real world. There is no evidence of EHL products triggering inhibitors in PTPs; normally inhibitors would not be expected in PTPs. However, it remains to be seen whether the absence of inhibitors will continue to hold true with PUPs.

The use of rFVIIIFc in immune tolerance induction yielded impressive results in a patient who did not respond to conventional ITI for many years, thus it has potential as improved treatment for patients with inhibitors. However, the ITI setting is complex as there are many variables and individual circumstances that make it different to draw and study data; a randomized component may be needed.

PANEL DISCUSSION: HOW WILL WE AFFORD NEW TREATMENTS?

CHAIR: MARK W. SKINNER, PRESIDENT, WFH USA; PAST PRESIDENT, WORLD FEDERATION OF HEMOPHILIA

With the introduction of new treatments and very promising but potentially expensive gene therapies in the development pipeline, a key challenge will be bridging the gap between state-of-the-art science and the realities of healthcare system fiscal constraints. As payers and health technology assessment agencies demand more data and evidence on therapeutic effectiveness, it is crucial for all stakeholders in the hemophilia community to help define the value and core outcomes of the novel therapies including gene therapy to support coverage and reimbursement decisions.

Sean Tunis, MD, CEO, Center for Medical Technology Policy (CMTP)

Affordability of treatment and rising healthcare costs are constant overarching concerns for healthcare payers everywhere around the world, said Dr. Sean Tunis. As novel therapies make it to market, policymakers and payers must decide whether to allocate limited healthcare dollars to cover expensive new therapies or instead to other medicines or interventions that could provide wider societal benefit for the investment. Therefore, it is critical for payers to understand the value of a new therapy and its comparable or improved effectiveness and health outcomes vis-à-vis existing treatments.

Harvard economist Michael Porter notes that in healthcare delivery, value is defined as health outcomes achieved relative to the costs. However, the measurement of value is complex as health outcomes are multidimensional and inherently specific to a given medical condition and intervention. A key challenge in clinical research is the lack of standardization of outcome measures and instruments across different therapies, medical conditions, and areas of healthcare. Gene therapy raises a new challenge in that the outcomes associated with a gene therapy "cure" may be different from the current standard of care.

The coreHEM project was initiated by the U.S. National Hemophilia Foundation, McMaster University, and the CMTP Green Park Collaborative. Through a multi-stakeholder consensus process, the goal is to identify a core set of outcomes to measure the effectiveness and value of gene therapy products in hemophilia. coreHEM stakeholders include clinicians, payers, patient advocates, epidemiologists, methodologists, academic researchers, government representatives, industry representatives, international health technology assessment agencies, and pharmaceutical companies developing gene therapy for hemophilia. So far, stakeholders have identified and ranked a range of outcomes and next will meet to review the results, identify consensus areas, and discuss differences of view. The same core outcomes and assessment tools need to be used across all gene therapy trials, to allow fair comparisons of outcomes and value. It is important to define and measure meaningful outcomes to help payers and health technology assessment agencies understand the value and pricing of gene therapies, as well as for patients and clinicians when making treatment decisions.

Jim Lennertz, Senior Vice President, Commercial, EUMEA, BioMarin

A key challenge in trying to move forward with market access for gene therapies is that healthcare systems are not currently set up to procure such high-cost curative therapies, even though arguably treatment cost is more predictable and can be offset over time, said Jim Lennertz. He gave a brief overview of Biomarin's single-infusion gene therapy for hemophilia A (BMN 270). A single intravenous dose is administered to deliver the functional FVIII gene to the patient's liver cells, which then have the ability to produce FVIII protein. It is currently under investigation in clinical trials. Clinical trial data show FVIII activity levels in or near to the normal range. It is estimated that a limited percentage of severe hemophilia A patients would be eligible for gene therapy at launch; as evidence matures, usage may expand to other patient groups.

Alternative funding strategies will be needed to achieve affordability and access. An ideal funding approach would meet a range of stakeholder needs: address uncertainty around long-term clinical effectiveness; fit within the payer's budget and financing needs; provide appropriate return on investment to support pharmaceutical innovation; provide justification for healthcare investment; and enable broad patient access to the gene therapy treatment. For health authorities and payers, important considerations for gene therapy coverage and reimbursement include: identifiable patient population, well-understood natural history, reliable biomarkers of clinical outcomes, and ability to offset costs. Hemophilia A meets all these key requirements for supporting patient access to gene therapy.

Different funding methods that could be used to fund high-cost gene therapies, depending on the health system, include an upfront payment, amortization (payment installments spread over a period of time), outcomes-based payments, and risk-sharing agreements (i.e., money back guarantees if expected outcomes are not achieved).

John Furey, Chief Operating Officer, Spark Therapeutics

The imminent arrival on the market of gene therapies with the potential for lifelong curative effects from a single treatment dose raises unique challenges in terms of how to assess their clinical value, estimate the long-term cost offsets, and establish what is fair pricing given limited clinical data and uncertainty on durability of effects. Stakeholders—manufacturers, payers, patients, and policymakers—need to work together to resolve these issues and develop new pricing and payment paradigms to address the critical issues of access and affordability, said John Furey, Chief Operating Officer of Spark Therapeutics.

Spark Therapeutics has developed a one-time curative gene therapy for inherited retinal disease that is poised to be among the first gene therapies approved in the United States (the FDA decision is expected soon). Spark also has gene therapies for hemophilia A and B in development.

Preliminary phase 1/2 data on investigational SPK-8011 for hemophilia A provide proof-of concept. Five patients were infused at three different doses. There were no spontaneous bleeds or serious adverse events reported in any of the patients as of August 2017, including no FVIII inhibitors and no thrombotic events. Preliminary phase 1/2 data on investigational SPK-9001 for hemophilia B show predictable results leading to a reduction of 96% in annualized bleeding rate and 99% in annualized infusion frequency as of June 2017 with cumulative follow-up of 9.6 patient years, and no serious adverse events reported to date.

There are several key factors in assessing the value of gene therapies with potential long-term or curative benefits: level of consistency of effect, level of predictability of results, and level of sustained expression. Important questions to consider in pricing a one-time gene therapy include:

- How can stakeholders ensure health economic modeling includes quality of life, indirect medical and societal costs, as well as recognition for longer-term durability of effect?
- How can focus be shifted from a pay-for-episode of care reimbursement model to a model that encourages and reflects development of one-time treatments that can deliver long-term benefits?
- What potential novel payment and reimbursement models can help address budgetary concerns to ensure patients get access to medicines they need?
- What role can pharmaceutical companies play to help ensure patients get the access they need?

In healthcare systems in Europe, and increasingly elsewhere in the world, incremental cost-effectiveness ratio (ICER) is used to assess the cost-effectiveness of a therapy or intervention in terms of the differences in cost and effects compared to another possible intervention. ICER analysis can encompass direct effects in terms of health outcomes as well indirect effects such as impacts on quality of life or societal costs.

However, healthcare systems are largely not set up to accommodate the market entry of many high-cost gene therapies for different diseases that are anticipated to arrive in the marketplace over the next decade, nor how to consider the profound implications on health outcomes and budget impact. Dialogue and collaboration is needed among gene therapy manufacturers, payers and other stakeholders to develop new pricing mechanisms, i.e., pay-for-performance and annuity payment mechanisms to ensure that patients have access to the best standard of care including possible lifelong cures.

Albert Farrugia, Senior Scientific and Regulatory Advisor, Kedrion S.p.A

Healthcare reimbursement strategies can be constructed with restrictive criteria that limit coverage for specific drug therapies as ways to manage use, control costs, or address certain needs, said Albert Farrugia. In health technology or cost-effectiveness assessment settings, there's an important difference between effectiveness in terms of a drug's efficacy according to the product label and effectiveness as defined by patient experience in real life. With gene therapies in hemophilia, key challenges to gaining market access are price and uncertainty of long-term safety and sustained effectiveness in the real world. Risk-sharing arrangements and technology leasing reimbursement strategies are ways to resolve such issues so that high-cost breakthrough therapies and genetic cures are affordable to payers and accessible to patients.

Risk-sharing arrangements and technology leasing reimbursement strategies are payment mechanisms in which the supplier receives payment only for delivered outputs rather than delivered products, which allows payers to take into account uncertainties in therapeutic outcomes and reimburse for healthy time rather than the product or technology. This is an important consideration when health technology assessment or reimbursement agencies have to study the added benefits or long-term effects of expensive rare disease treatments and decide on their value and affordability.

There are evolving perspectives on the affordability of gene therapy for hemophilia. There are existing factor replacement therapies, as supported by extensive clinical data on outcomes, longevity and quality of life of people with hemophilia. The endpoints of gene therapy are reasonably unequivocal but there is debate on annualized bleeding rate as the primary endpoint. In addition, there is uncertainty regarding effectiveness versus efficacy, tolerization, and durability of treatment. Risk-sharing models and alternative payment strategies are ways to address the issues to make new therapies available to patients.

Discussion

There are substantial challenges that need to be addressed to advance hemophilia gene therapies from clinical trial to the marketplace—the uncertainty of the estimated clinical effects and curative potential as well as the related challenges of establishing value, price and payment mechanisms to make gene therapy affordable and accessible in health systems, noted chair Mark Skinner. Hemophilia patients and clinicians are tasked with helping define the outcomes and added benefits of gene therapy and the life-changing value of a cure to patients. Do payers give weight to the outcomes that patients really value beyond health status or do decisions come down to clinical effects, cost, healthcare budget, and willingness and ability to pay?

While business and economics are dominant and prevailing forces, with pharmaceutical companies concerned about return on investment and payers preoccupied with how to minimize healthcare spending, what matters to patients does matter to them as well, Dr. Sean Tunis said. Payers and policymakers are influenced by public pressure when it is well supported, therefore it important to be able to systematically measure and quantify both the clinical and qualitative outcomes that are meaningful to patients and their families.

Another challenge is that limited clinical data is available at market authorization, yet it is essential to ensure that payers and health technology assessment agencies take into account the longer time horizon of gene therapies and assess value in terms of the whole-of-life benefits and savings from what could be a potential cure from a single treatment. Pharmaceutical companies increasingly try to address these issues earlier in the clinical trial process through dialogue and meetings with regulators and payers on the outcomes and evidence required to gain market access, John Furey said. Following market approval and licensing, payers and manufacturers can negotiate performance-based payment agreements based on the mutually defined outcomes demonstrated in clinical trial. Jim Lennertz noted that payers typically focus on benefits demonstrated during the period of time of the clinical trial, but it is important for reimbursement systems that use upfront payment to estimate benefits over longer time horizons.

Definition of value, benefits and desired endpoints depends on the specific population in question, said Albert Farrugia. This leads to the question of what patient populations would benefit most from gene therapy; the value and outcomes are quite clear with previously untreated children, whereas endpoints are less clear and universal for older patients, for whom quality of life outcomes might depend on their individual circumstances and existing morbidities.

Dr. Tunis noted that numerous participants in the coreHEM project emphasized the importance of taking into account the particular value of potential cures to patients. As the emerging field of gene therapy grows, better measures of patient-valued outcomes need to be built into the system.

HUMANITARIAN AID: PRIMING THE PUMP – WHAT NEXT?

CHAIR: GLENN PIERCE, MD, PHD, LA JOLLA, CALIFORNIA, USA; WFH MEDICAL ADVISORY BOARD MEMBER

The WFH's expanded Humanitarian Aid Program has already had remarkable effects since its rollout in 2015, with a tenfold increase in the amount of factor concentrates distributed worldwide, and profound impacts on thousands of lives. This session gave a snapshot of the program's expanded capacity and reach and the experiences in Egypt and Senegal, where WFH aid is helping strengthen national hemophilia care.

WFH Humanitarian Aid Program: The global commitment

ASSAD HAFFAR, MD, DIRECTOR, HUMANITARIAN AID PROGRAM, WORLD FEDERATION OF HEMOPHILIA

The WFH Humanitarian Aid Program was started in 1996 with the aim of helping people with hemophilia in developing countries with very little or no access to treatment products, through the distribution of surplus factor concentrates donated by pharmaceutical companies, which were designated for emergency treatment and short-term medical needs. The program grew as product donations increased over the years, with over 266 million IUs of factor concentrates distributed to 87 countries by 2015. But there were challenges due to the largely ad hoc nature of donations; as a result, the WFH had limited notice and control regarding donation quantities, product shelf life, shipping and customs logistics, and other aspects important to optimal program planning. The expansion of the program was driven by the goal of having sustained levels of product donations and greater predictability of donation quantities and timeframes, to allow WFH to expand the magnitude and scope of its humanitarian aid in the developing world.

Since 2015, the expanded Humanitarian Aid Program has had an upsurge in product donations, with major impacts on access and treatment options for patients in the developing world. In the past, due to limited and fluctuating amounts of product donations, the WFH stipulated that recipient countries use humanitarian aid products only in two cases: acute bleeds and life-threatening surgeries. Now that larger quantities are available, donated factor products can also be used for preventive surgeries, prophylaxis, and immune tolerance induction. Thus donated products are now being used for surgeries such as intracranial bleeding and other life-threatening trauma, open synovectomy, and circumcision. The availability of donated products for prophylaxis is transforming the lives of children in a number of countries; in Pakistan, a prophylaxis program for children under 5 years of age was initiated in Lahore and is being extended to other parts of the country. Humanitarian aid products are also being used for immune tolerance induction in several cases around the world.

In 2015, the WFH distributed about 53 million IUs of factor concentrates—this increased to 141 million IUs in 2016 and 170 million IUs at the end of the third quarter of 2017. About 16,000 people with hemophilia have been treated with donated products during this time, including for 31,000 acute bleeds as well as for 467 surgeries; in addition, 1,200 patients benefitted from prophylaxis. Beyond donations of treatment products, the Humanitarian Aid Program also coordinates training workshops on fundamental topics such as laboratory diagnosis, patient outreach, and bleed management to help ensure that local infrastructure and medical expertise are in place and donated products will be appropriately used.

The WFH's corporate partners are critical to the expansion of the Humanitarian Aid Program. Visionary contributors Bioverativ and Sobi have made multi-year commitments of product donations and financial support for delivery logistics and programming. Contributors include Grifols, CSL Behring, Green Cross, Biotest, Project Recovery/Canadian Blood Services, and Project Wish/Italian National Blood Centre.

Effect of humanitarian aid on treatment practices in Africa

SALIOU DIOP, MD, HEAD, BLOOD BANK AND TREATMENT CENTRE, SENEGAL; WFH MEDICAL ADVISORY BOARD MEMBER

Dr. Saliou Diop described the scarcity of treatment in Africa and main impacts of the WFH Humanitarian Aid Program on hemophilia care, and key challenges that need to be addressed. There are 19 sub-Saharan African countries accredited as WFH national member organizations, among 134 NMOs worldwide, with 4 more African countries to be accredited at the 2018 WFH Congress.

Data from the 2015 WFH Global Survey on the number of identified inherited bleeding disorder patients per region show only 11.4% of expected cases in Africa had been identified. Among sub-Saharan African countries, less than 70% had laboratory hemostasis expertise, less than 50% had medical follow-up, and only about 20% had multidisciplinary care for bleeding disorders. Most factor concentrates used in the region came from humanitarian aid; purchase of these expensive blood products is exceptional. WFH data on estimated global use of FVIII in 2015 show that FVIII consumption in Africa was only 2% of the total global usage, although Africa comprises 16% of the world's total population. Thus far only two countries, Mauritius and South Africa, have FVIII usage of more than 1 IU per capita. In most countries, FVIII usage is less than 0.1 IU per capita, mostly product donations from WFH humanitarian aid. Organization of hemophilia care delivery is nascent in many African countries, therefore morbidity and mortality are high and chronic complications are very frequent. However, progress continues with identifying new patients.

Over the past 15 years, 26 sub-Saharan African countries received donations from the WFH Humanitarian Aid Program. In 2016, the WFH distributed more than 18 million IUs of factor concentrates in the region; a similar amount is projected for 2017. The WFH also provided clinical training on factor concentrate therapy and other aspects of hemophilia care, and developed factsheets on low-dose prophylaxis, the use of extended half-life factor products in countries with limited resources, and diagnosis and management of inhibitors. These activities have advanced hemophilia care in the region and are valuable in advocacy for government procurement of factor concentrates and for comprehensive hemophilia care. Increased WFH product donations over the past two years have supported an increase in surgical options and procedures, and allowed the introduction of low-dose prophylaxis programs, benefitting 75 patients to date.

There are a number of challenges and priorities moving forward. To ensure accurate diagnosis, there must be medical training (e.g., centre twinning), and laboratory facilities, resources, and quality assurance (e.g., IEQAS). To improve patient care and follow-up, development of patient registries, multidisciplinary care, and national hemophilia care will be needed. Finally, advocacy for government procurement of factor concentrates is critical to ensure long-term and sustainable hemophilia care in Africa.

Egypt: Model for humanitarian aid delivery

MAGDY EL EKIABY, MD, HEAD, BLOOD TRANSFUSION CENTRE & HEMOPHILIA TREATMENT CENTRE, SHABRAWISHI HOSPITAL, EGYPT

The organization of hemophilia care in Egypt is the outcome of many years of work and collaboration between the Egyptian Hemophilia Society and WFH, along with health authorities, blood services, and university hospitals. Egypt currently has 4,504 patients with hemophilia A, 1,205 patients with hemophilia B, 543 patients with von Willebrand disease, and 1,045 patients with other rare bleeding disorders. In 2016, the WFH donated a total of 1.7 million IU of rFVIIIFc (Eloctate) and 0.6 million IU of rFIXFc (Alprolix). The total available product in 2016 was in the range of 25 million IU. Other treatment products used include solvent detergent cryoprecipitate FVIII (8 million IU in 2016), non-virally treated cryoprecipitate (close to 100,000 IU each year) and fresh frozen plasma. In 2017, WFH donations included 7.5 million IU of rFVIIIFc and 4.25 million IU of rFIXFc.

The biggest portion of humanitarian aid products goes toward the treatment of acute bleeds, mostly joint bleeds, with over 2,000 bleeding episodes treated in 2016 and 2017. Donated products are also used in the management of serious bleeds, such as intracranial hemorrhage, psoas muscle bleeds, and severe gastrointestinal bleeding. They are also used in a range of surgical procedures and orthopedic procedures including correction of joint deformities and corrective surgeries for the knee and elbow. So far, WFH product donations have not been used for prophylaxis, but low-dose prophylaxis for children is currently under discussion with HTCs.

Donated factor product is also being used for immune tolerance induction in an ongoing case of a patient with FVIII inhibitors, who has had no FVIII recovery after many months of therapy. This highlights the challenges of deciding how to use humanitarian aid products: is ongoing ITI affordable or would it be more effective and beneficial to more patients to use donated products for surgical procedures and prophylaxis? Health authorities have the responsibility of setting the parameters for the use of humanitarian aid products.

WFH humanitarian aid has helped bring about strong government commitment towards the hemophilia community. Egypt's procurement authority has issued an international tender for 40 million IU in 2018 (with expected price of US$ 0.14–0.20 cents). Domestic production of solvent detergent cryoprecipitate is expected to be 12 million IU FVIII in 2018. Overall, Egypt is expected to increase its product supply from 0.25 IU per capita to 0.5 IU per capita in 2018.

Humanitarian aid donations have increased the availability of treatment and improved access to tertiary care, including the treatment of serious bleeds, orthopedic surgery, general surgery, and immune tolerance induction. However, much more progress is needed. In 2016, Egypt's procurement and local production of factor concentrates was about 0.25 IU per capita. In 2018, the WFH is expected to donate an estimated 5.5 million IU of factor concentrates to Egypt; however, Egypt needs a minimum of 90 million IU to reach the target of 1 IU per capita.

Discussion

Dr. Glenn Pierce noted that in Senegal, only about 10% of patients with hemophilia have been diagnosed. Many patients with severe diagnosis go undiagnosed because they die quite young and there is also a lack of accurate diagnosis, Dr. Saliou Diop said. Continued training of clinicians and laboratory technicians is needed, along with increased availability of treatment products in order to improve diagnosis and care.

Dr. Steven Pipe noted the small quantity of bypassing agents distributed through the Humanitarian Aid Program, while 170 million IUs of factor were distributed in 2017, and said it is unlikely that inhibitors have not been triggered by factor concentrates donated through the program. Dr. Assad Haffar said there are a number of ITI cases in developing countries but efforts to emphasize the need for more donations of bypassing agents have not been successful so far. Dr. Marijke van den Berg stressed the importance of collecting immunogenicity data and clinician training on inhibitor risk and management in developing countries.

Thomas Sannié, president of l'Association française des hémophilies, emphasized the crucial role of national member organizations in raising awareness of hemophilia and other inherited bleeding disorders across the country in order increase diagnosis. It is also important to conduct publicity campaigns in multiple languages for the broadest reach possible, so that everyone has the opportunity to learn about bleeding disorders and perhaps recognize the symptoms in their child and come to the HTC. Strong collaboration between the patient organization and medical community is also essential to increase diagnosis.

ENSURING ACCESS TO AFFORDABLE TREATMENT PRODUCTS

CHAIR: ALAIN WEILL, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA

There are many barriers that can impede the ability of countries to achieve minimum standards of care and levels of factor use. The biggest barriers pertain to cost price and economics, and ineffective tender and procurement processes. This session showed how international coalitions are changing the global landscape for factor concentrates through strategic humanitarian aid aimed at ensuring predictable and sustainable national hemophilia care.

The EHC Partners Program

BRIAN O'MAHONY, CHIEF EXECUTIVE, IRISH HAEMOPHILIA SOCIETY; PRESIDENT, EUROPEAN HAEMOPHILIA CONSORTIUM

With its new program PARTNERS: Procurement of Affordable Replacement Therapy – Network of European Relevant Stakeholders, the European Haemophilia Consortium has set a determined goal of helping countries with very low factor usage access better FVIII and FIX prices in order to increase the availability of treatment and per capita use. Brian O'Mahony presented the program rationale and framework.

The latest EHC member survey in 2015 found wide-ranging prices for factor concentrates in European tender and procurement systems, with a fourfold difference in recombinant FVIII prices and a sevenfold difference in plasma-derived FVIII prices. The survey results also revealed statistically significant lower prices for factor concentrates when hemophilia clinicians and patient organizations were involved in national tenders. With this data, the EHC successfully pushed for the new recommendations for optimal use of clotting factors subsequently set forth by the European Directorate for the Quality of Medicines and Healthcare (EDQM) in 2016:

- The minimum consumption of factor VIII concentrate in any country should be 4 IU per capita of general population.
- The minimum consumption of FIX concentrate in a country should be 0.5 IU per capita of general population.
- National or regional tenders for factor concentrates are encouraged and should always include both hemophilia clinicians and national hemophilia patient representatives.

The Partners Program aims to help countries with low factor usage gain access to factor concentrates at more affordable prices and achieve sustainable increases in factor use. The eligibility criteria include:

- Country currently uses less than 4 IU per capita of FVIII
- Country currently uses less than 0.5 IU per capita of FIX
- Country where all children with severe hemophilia are not on prophylaxis
- Country has a national tender or procurement process
- Government, clinicians and the NMO agree to participate in the program and have mandatory clinician and NMO representation on the tender board

The Partners Program aims to help countries improve their procurement processes and hold three-year tenders to gain access to factor concentrates at significantly lower prices and purchase larger quantities. A maximum ceiling price is set at €0.17 per IU, which is a discount of at least 70% on median FVIII and FIX prices from the last tender survey. A tender purchase would cover the three-year term and countries must purchase more than their current amounts and increase per capita factor consumption, towards achieving the EDQM recommendations of at minimum 4 IU FVIII per capita and 0.5 IU FIX per capita.

There are 14 European countries that meet the program criteria: Albania, Armenia, Azerbaijan, Belarus, Bosnia-Herzegovina, Bulgaria, Estonia, Kyrgyz Republic, Latvia, and Macedonia. The program's potential impact is great: if these 14 countries double their per capita FVIII consumption from their current use, it would increase overall consumption by 175 million IU per year; if factor use increases to 4 IU per capita, overall FVIII use would increase by an additional 390 million IU per year. Governments cannot use the program to purchase the same current amounts of factor at lower prices and thereby save on per unit cost; it is stipulated that hemophilia expenditures must remain the same or increase (i.e., they must purchase greater quantities).

To date, the Partners Program has signed on three pharmaceutical companies: Kedrion, Pfizer, and Sobi. EHC representatives so far have visited Serbia, Ukraine, Kyrgyz Republic, Albania, Bulgaria, Romania, Latvia, and Macedonia. Operational discussions are underway to address key issues within the local contexts, such as product registration and licensing, regional purchase and distribution, and treatment guidelines. The program officially launches in European Parliament on November 28, 2017.

Access to hemophilia care – post humanitarian aid

ALBERT FARRUGIA, SENIOR SCIENTIFIC AND REGULATORY ADVISOR, KEDRION S.P.A

Albert Farrugia described some challenges and barriers that impede efforts towards achieving global availability of factor concentrates and affordable access to treatment for all, and emphasized the untapped potential and capacity within existing blood collection and plasma fractionation systems to address these needs and the actual waste of factor components available in plasma currently recovered from donated blood but not being fractionated. To increase global supply and access, strategies are needed that take into account the many different stakeholders and interests in blood services delivery.

Despite steady and increasing worldwide demand for plasma-derived FVIII concentrates over the last three decades, estimates show that much of the factor available in plasma from blood collection is not extracted and therefore not reaching patients. In 2014, a total of 45 million litres of plasma was collected globally; using current technology, which has an expected yield of 200 IU of FVIII per litre of plasma, this would result in 9 billion IU of plasma-derived FVIII concentrates. However, in reality only 4 billion IU of plasma-derived FVIII concentrates were actually provided in 2014; therefore, only half of the possible and available amount of factor proteins was converted into factor concentrates. In contrast, similar estimates for other plasma-derived products indicate that about 85 per cent of the available immunoglobulin and albumin is being extracted from plasma collected. Most of the plasma factor is discarded from manufacture because it is deemed nonsalable.

New approaches to donation of factor therapies for international humanitarian aid, based on a convergence of all stakeholders and their interests, are helping improve the global plasma landscape. Over the past years, Italy's Project Wish has donated over 10 million IU of factor concentrates manufactured from excess plasma components in the Italian blood collection system to countries such as Afghanistan, Albania, and India. In June 2017, the Italian National Blood Centre signed an agreement with Armenia**'s** Ministry of Health on the donation of over 750,000 IU of factor concentrates derived from donated plasma exceeding Italy's requirements. The agreement includes cooperation on developing standards for optimum use of blood components in Armenia, introduction of a national blood collection system, and research projects and exchange of information. Technical and logistical support is provided by Kedrion.

Despite this Italian model of success, similar efforts have not yet been initiated by other countries with the same blood system capacities and abundance of plasma components not being transformed into factor concentrates. Countries such as France, the Netherlands, Spain, and Australia all have publicly funded

national blood collection systems, plasma collection and fractionation at levels of national need, and primarily deliver recombinant products for hemophilia care and therefore have an excess of high-quality donated factor. More can be done to increase factor supply with available science and donated blood.

Better understanding of the features and dynamics of factor pricing could help improve access to treatment. Careful analysis is needed when comparing price and cost of novel agents to standard therapies, taking into account the impacts of infusion frequency and dosing. A 2015 analysis of longer-acting FIX that assessed and compared three label prophylaxis dosing regimens showed the strategies are not equivalent in terms of the factor dosage used, infusion frequency, and cost. Two strategies with different dosing and frequency had a cost difference of $13,900 per dose, different trough levels and peaks, and substantially different annual factor usage. Ultimately, the science and technology exists to provide better care; the benefits, costs, and willingness to pay need to be weighed.

Biosimilars, i.e., generic versions of off-patent biological drugs, present an opportunity to improve access to affordable care. EU data show the introduction of biosimilars has resulted in substantial drops in price for many drugs. Generally, the entry of biosimilars in the market increases competition, which leads to price reduction that affects not just the prices of the reference products, but also on the total market price of the product class as a whole. Yet while a number of biosimilar factor concentrates have been introduced, mostly in markets in developing countries, there have not been drops in price as seen with other therapeutic drugs. Development of biosimilar recombinant factor underway in Russia may bring about the price reductions and increased factor availability hoped for and necessary to achieve global access. However, resistance to the concept of biosimilarity in factor concentrates is evident from both industry and regulators, and in the recent decisions of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) regarding the relationship between product type and inhibitor risk. These principles may impede access to products in poorly resourced countries by increasing the regulatory burden.

Discussion

The WFH's Humanitarian Aid Program, Global Alliance for Progress, and other development programs are effectively making inroads in developing countries with very inadequate or no access to treatment, noted Mark Skinner. Could the Partners Program potentially be extended to other parts of the world as part of a continuum of development programs to advance and accelerate progress in the developing world? Should the Partners Program prove to be successful in Europe, it would likely work in other countries as well, Brian O'Mahony said. A combination of different approaches is needed to achieve global treatment for all; no single approach will work on its own.

It is important to ensure that there is adequate supply and availability of factor concentrates so that physicians are able to prescribe factor therapy, said Dr. Cedric Hermans. Many physicians left the field due to lack of available treatment—sustainable supply is critical to attracting new physicians. Albert Farrugia noted that despite overall access level in India being low, clinical efforts by centres of excellence have produced results in areas such as low-dose prophylaxis and immune tolerance induction. Logistical hurdles in such countries pose formidable barriers to access, but the core problem is lack of access to factor concentrates resulting in low supplies and poor patient outcomes. This is currently measured in terms of IU per capita, but an additional assessment of factor usage per patient is more informative and can highlight additional challenges; in countries with high per patient usage coupled with low overall usage per capita, this can indicate low levels of diagnosis, probably coupled with inequitable access based on income and class.

PANEL DISCUSSION ON TROUGH LEVELS

CHAIR: ALOK SRIVASTAVA, MD, DIRECTOR, HEMOPHILIA TREATMENT CENTRE, CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

With the emergence of extended half-life factor concentrates in some markets and novel bypassing agents and gene therapies advancing closer to reality, in some ways, the global hemophilia community is re-examining existing philosophy and paradigms of treatment, said Dr. Alok Srivastava. There is recognition that current minimum standards for prophylaxis which target 1% trough levels are neither ideal nor adequate to prevent spontaneous bleeding and hemarthrosis, and definitely need to be revisited.

Margaret V. Ragni MD, MPH, Director, Hemophilia Center of Western Pennsylvania, USA

Gene therapies for hemophilia anticipated to become available in a few years will transform treatment, outcomes and way of life for patients, and compel rethinking of the concepts of hemophilia outcomes and endpoints, said Dr. Margaret Ragni. Annualized bleeding rate has long been the primary endpoint in clinical trials for regulatory approval as well as in clinical practice. Gene therapy, however, enables patients to achieve sustained long-term factor expression at levels that provide full protection from spontaneous bleeding; trough level and annualized bleeding rate are no longer as important and relevant endpoints.

Prophylaxis with factor concentrates is based on the concept of achieving a minimum trough of 1% factor activity levels in order to prevent spontaneous bleeds, with the primary endpoint being annualized bleeding rate. But all the new types of therapy demand re-examination of the concept of endpoints. With gene therapy, it is possible to attain sustained 10-30% factor activity levels, which allow for much more unhindered activities as there are no peak or trough levels, while annualized bleed rates are reduced to near zero. There are also no infusion and adherence issues. The arrival of these novel therapies for hemophilia requires a shift from the conventional definitions and paradigms.

The goal of gene therapy is to achieve sustained long-term expression of factor levels. In the past, optimum trough level has been defined as maintaining at least 5% FVIII and FIX activity levels; whereas the aim now with gene therapies is to achieve sustained factor expression with at least 15% FVIII and FIX activity levels for the absence of joint bleeds and levels above 30% for surgery. With conventional treatment, factor level and annualized bleeding rate are objective endpoints. Defining the endpoints in gene therapy is more complex and may need to focus more on patient-related outcomes such as quality of life, happiness, physical activity and sports participation, and even normal life.

Important questions that need further discussion and investigation include:

- What are the criteria for “success” in prophylaxis, gene therapy and novel bypass?
- What is the role of age, weight, activity and cardiovascular risk in this decision?
- How high should peaks, and how low should troughs go? What are risks and balances?
- What is the ideal trough to attain with gene therapy?
- Is there a level that allows differentiation of joint pain and acute bleed?
- Is elimination of peaks and troughs by novel bypass a concern? Do patients undergoing surgery require reassessment of peak, trough and inhibitor level?
- As patients age, what checks and balances should be in place for those maintaining 30-50% levels? What cardiovascular markers should be monitored?
- What future prospective studies will be needed to help answer these questions?

Cedric Hermans, MD, Head, Haemophilia Centre, Saint-Luc University Hospital, Brussels, Belgium

The classical rationale for prophylaxis in hemophilia is to maintain at least 1% FVIII/FIX activity in order to prevent spontaneous bleeding and particularly hemarthrosis, based on clinical observation that patients with moderate hemophilia (2–5% FVIII/FIX level) generally have much fewer joint bleeds than patients with severe hemophilia (< 1% FVIII/FIX level). However, studies and patient outcomes clearly show that a target trough of 1% is not enough to prevent bleeding episodes since patients with 1% factor levels continue to have spontaneous bleeding and joint bleeds. Evidence suggests FVIII activity level needs to be maintained above 10% to prevent joint bleeds; the question is whether this is an achievable goal today.

There are other underlying reasons for a target trough of 1% in prophylaxis that are based on the half-life of standard factor concentrates, convenience (FVIII infusion every 2-3 days, whereas greater frequency could decrease total amount used), and cost-effectiveness (a trough of 2% would require a higher amount of factor). Maintaining FVIII activity level above 1% with current factor concentrates can be challenging because it relies on patient pharmacokinetics. When factor is infused, factor activity rapidly increases and peaks, then drops relatively quickly to baseline factor level or trough level. However, there are significant individual variations in FVIII half-life/pharmacokinetic response, factor activity level, and time spent below 1% FVIII, which affect risk of breakthrough bleeding. There are many requirements for success with this prophylaxis strategy based on 1% trough: appropriate individualized treatment regimen (i.e., dosing and frequency), availability of reliable FVIII assays**,** individual pharmacokinetic assessment, patient adherence to treatment**,** and regular follow-up.

With standard factor concentrates, a target FVIII level above 5% can only be achieved through more frequent infusions or higher doses in patients with good venous access and perfect adherence. Overall, there is limited opportunity to raise trough level with standard factor concentrates. With extended half-life factor concentrates, however, higher FVIII trough and activity levels can be achieved using the same dosage and frequency as standard factor therapy; and the same time above the standard 1% trough threshold can be achieved with less frequent infusion.

Individualized prophylaxis regimens are needed given that hemophilia phenotype is heterogeneous and influenced by factors such as joint status, life style and physical activities, coagulation balance and co-inheritance of thrombophilic traits, and other genetic factors. Another challenge is determining the most important pharmacokinetic parameters to follow. Peak/time spent in reduced bleeding risk zone is important to prevent activity-related and traumatic bleeds and trough level is important to prevent spontaneous breakthrough bleeds, while area under the curve can be taken into account to prevent subclinical bleeds, maximize the window of protection, and reduce the bleeding risk zone.

Maintaining factor levels above 1% is a minimum objective of prophylaxis with standard factor concentrates. With the new treatment options, the aim should be to provide treatment options that allow patients to achieve steady clotting potential close to normal levels without major burden. However, the objectives and targets need to be better defined.

Mark W. Skinner, President, WFH USA; Past President, World Federation of Hemophilia

Prophylaxis in hemophilia and key concepts on its value and use were pioneered in the 1960s, as described in a 1962 *Haemophilia* paper by Dr. Inga Marie Nilsson on the Swedish experience with 1-3% trough levels. It can be argued that prophylaxis concepts applied in practice today are far from new and reflect the state of science 50 years ago, in conditions of limited knowledge and treatment, said Mark Skinner. In the decades since, there have been major treatment advances and increased availability and access; as a result, the concepts surrounding prophylaxis have evolved. Indeed, today it be can said that a trough of 1% is minimally effective to prevent bleeds and joint damage, and was never intended as optimal treatment.

At the 2012 World Hemophilia Congress, as outgoing WFH President, Mr. Skinner stated that patients and clinicians have been conditioned to accept converting a patient's phenotype from severe to moderate as the desired endpoint, which has been interpreted to be maintaining a baseline factor level above 1%. But while there have been advances in all aspects of treatment (clinical and laboratory diagnosis, comprehensive care, home infusion therapy, viral inactivation and other safety measures, recombinant therapy etc.), the evidence clearly shows that a trough of 1% is inadequate to fully prevent bleeding that leads to joint damage. Given treatment advances and that normal FVIII/FIX activity is 50–150%, he proposed a paradigm shift—an aim of 15% factor levels to prevent bleeding to a degree that more closely mimics a normal state in the absence of hemophilia.

Although the concept of the 15% trough level and aspiration for absence of joint bleed seemed unrealistic at the time, it was supported by a 2011 study that showed the association between joint bleeds and factor level; patients with below 5% factor levels had the highest risk for joint bleeds, and patients with factor levels of 10% and higher had a very low risk, which approximated to no expected joint bleeds in patients with over 15% baseline factor activity levels.

How to achieve zero bleeds really matters to patients. In the past, restricted physical activity and sedentary lifestyles were ways to minimize bleeding. Today, gene therapy offers the possibility to correct the clotting deficiency to normal and enable people with hemophilia to live normal lives, with the same freedom and spontaneity as others. Moving forward, it can be argued that minimally effective therapy is no longer the appropriate standard of care for hemophilia. The goal of treatment in 2017 and beyond should be based on patient-centred values, with individualized prophylaxis tailored to individual preferences and needs. Aiming for a 15% trough would provide a level of protection that allows people with hemophilia to have normal aspirations and fully pursue opportunities in life.

Discussion

Prophylaxis is highly effective if well managed but 1% trough does not represent normal—people without hemophilia have factor levels above 50% and annualized bleeding rate is zero, said Dr. Marion Koerper. The goal then for hemophilia patients should be 50% factor levels as anything less does not achieve normal. Given variation in individual pharmacokinetic response, individual PK studies are needed to tailor individual prophylaxis to the optimal dose and interval needed by the patient to be able to achieve a 50% trough level; this is time-consuming but achievable if clinicians work at it.

The general consensus in the audience seemed to be that the current model of treatment and prophylaxis rationale of maintaining factor level above 1% for bleed prevention is outdated. However, 50% trough levels are not currently possible in many parts of the world, and may not be possible without global availability of gene therapy, Dr. Alok Srivastava said. Until then, what should be the minimum standard and trough level with currently available therapies? Now that extended half-life concentrates have entered the market, there are new possibilities to refine the goals to address different situations, age groups etc.

In the current conditions, in which the majority of people with hemophilia around the world have little or no access to factor concentrates, an aim of 15% trough is not realistic, said David Page of the Canadian Hemophilia Society and chair of the WFH Coagulation Product Safety, Supply and Access Committee. While the current 1% trough target is far from adequate, the ideal trough level is best determined by the clinician and patient based on the treatment outcomes the patient hopes to achieve. Brian O'Mahony of the European Haemophilia Consortium said it is important to set high goals, collect data, and use the evidence to advocate for better standards; EHC efforts led to European adoption of higher minimum standards for per capita factor use, which should gradually increase factor consumption.

While extended half-life concentrates present greater possibility of aiming for 15% trough levels, without a fundamental shift in the pharmaceutical industry to a volume-based pricing model, a 15% trough level will not be possible with standard factor therapy, said Mr. Skinner. Pharmaceutical companies need to be convinced to shift their business model from margin-based profit to volume-based profit. Dr. Glenn Pierce agreed that costs need to decrease but cautioned that even should pharmaceutical manufacturers adopt volume-based pricing and substantially lower factor prices, it does not necessary follow that governments would continue to spend the same amount on hemophilia therapies; in all likelihood they would opt to save and spend less.

Dr. Margaret Ragni said implementing EHL therapies at her clinic has revolutionized thinking about what can be achieved through therapy—young children are able to be much more active and fully participate in sports because their dosing regimen is tailored to a higher protective trough level so that they have no bleeds. However, there is some backlash from insurers wanting to constrain factor use.

While prophylaxis clinical trials have conventionally used a minimum 1% trough level, in clinical practice the percentage level is not the relevant endpoint—the ideal goal is to allow to live bleed free and without limitations, Dr. Ragni said. However, some patients do well at 1-2% factor levels, with no breakthrough bleeds. It is important to discuss with patients whether their treatment allows them to do what they want to do; a questionnaire could be useful. Dr. Cedric Hermans agreed that for clinicians, the fundamental goal of therapy is to prevent bleeding, not 1% trough level. He makes clear to patients that there is zero tolerance for any bleeding—a bleed is treatment failure and must absolutely be avoided.

Matthew Jackson of the Canadian Hemophilia Society said he has moderate hemophilia B with 1-2% factor level and bleeding symptoms similar to severe hemophilia. He is on prophylaxis with plasma-derived factor and has not yet been able to switch to extended half-life factor because patients with severe hemophilia are the priority. There is discussion of giving priority to severe hemophilia when gene therapy is introduced but a 1% cutoff would exclude patients like him. The 1% definition for minimum factor/target trough level is problematic and should be refuted. Dr. Srivastava added that it is well recognized that patients with moderate hemophilia who have 1-2% factor levels can have symptoms similar to the severe phenotype.

The session closed with an audience poll on what trough level should be recommended in prophylaxis therapy with standard and EHL factor concentrates: 12% voted for >3% trough level; 32% voted for >5% trough level; 12% voted for >10% trough level; 23% voted for >15%; 21% voted for >30% trough level.

UNMET NEEDS AND UNFINISHED BUSINESS IN GENE THERAPY

DAVID LILLICRAP, MD, DEPARTMENT OF PATHOLOGY & MOLECULAR MEDICINE, QUEEN'S UNIVERSITY, KINGSTON, CANADA

Since 2015, several gene therapies in clinical trial have achieved therapeutic FVIII and FIX levels producing impressive hemostatic effectiveness and outcomes in hemophilia patients. However, thorough ongoing and long-term research will be needed.

Known knowns and known unknowns on the path toward a cure

GLENN PIERCE MD, PHD, LA JOLLA, CALIFORNIA, USA; WFH MEDICAL ADVISORY BOARD MEMBER

With the potential licensure of gene therapies for hemophilia possibly setting the path towards a cure, it is critical for patients, clinicians, and all other stakeholders in the hemophilia community to have a good understanding of this new type of treatment, what is known and unknown, and key challenges that need to be solved, said Dr. Glenn Pierce. There are different approaches to gene therapy for hemophilia, which have different implications in terms of efficacy, safety, and success. Gene therapy involves transferring a new gene into the cell nucleus; there is no removal or modification of the existing DNA sequence. Gene editing corrects the faulty gene or inserts the correct gene in its place. Cell therapy transplants whole cells, which may be subjected to gene editing before delivery.

Development of gene therapies using AAV vectors have been driven by the promise shown in terms of AAV uptake, transport, and uncoating, as well as vector genome persistence, transcriptional activity, and immune response. However, there are safety and manufacturing hurdles that need to be overcome. Dr. Pierce gave a brief overview of the AAV genome and construct of the AAV vector, evolution of AAV drug research and development, and the prevalence of pre-existing neutralizing antibodies to different AAV serotypes and variations in immune response in different populations.

Various components of AAV vectors interact with the patient in determining the outcome of gene transfer; the total capsid dose, genome, and transgene product could contribute to vector immunogenicity in some patients and affect gene transfer outcome. Variables in AAV-host interactions include: limited stimulation of innate and transgene immunity; capsid intracellular persistence and processing time course; dose dependence of immune response and transgene expression; source of inflammation in target organ; and inter-individual HLA phenotypes.

Work needs to be done to standardize AAV antibody assays and fulfill good manufacturing practices (GMP) before the AAV gene therapies are commercialized, including process development and scale up, product and impurity characterization, assay development, and final product definition and risk analysis.

The "known knowns" of AAV gene therapy include:

- need for "high" doses
- some occurrence of integration
- some acute subclinical liver toxicity
- heterogeneous transduction
- individual variability in protein production
- packaging size limitations
- pre-existing immunity
- not possible for young children
- manufacturing not scaled up (purification and quality control assays variable, not standardized)

Better understanding is needed about "known unknowns" including:

- long-term safety and implications of mild acute liver toxicity
- consequences of some integration
- durability of transgene protein expression
- vector cell-binding process

Gene therapies require continual research and long-term follow-up beyond clinical development and initiation of therapy. Education is critical and patients, clinicians, and providers have an obligation to get informed and understand the issues as gene therapies move through clinical trial towards market approval.

How to judge the efficacy of gene therapy trials

MARIJKE VAN DEN BERG, MD, PHD, VICE PRESIDENT MEDICAL, WORLD FEDERATION OF HEMOPHILIA

The past five years has seen intense development of novel technologies, bypassing agents, and gene therapies for hemophilia. As they move through clinical trials towards market authorization, it is essential to approach these novel types of medicine with absolute caution and thoroughly examine all safety aspects in order to ensure utmost safety and protection of patients, said Dr. Marijke van den Berg.

Data from the 2016 WFH Annual Global Survey shows that despite steady increase in FVIII use over time, there is still a very large gap in per capita factor use between upper-income countries and middle- and low-income countries. Although European countries have relatively high incomes and high mean factor usage compared to other parts of the world, there are still significant gaps in per capita use. Meanwhile, it's clear there is a lack of diagnosis and inadequate treatment available in low-income countries, which are both challenges and opportunities to improve and expand hemophilia care.

There are a number of burdens of prophylaxis using currently available factor concentrates including: frequent infusions, delay in start of prophylaxis, high costs, adherence, and inhibitors. Novel therapies and gene therapies in hemophilia hold a lot of promise for reducing some of these burdens. Extended half-life factor products will allow lower infusion frequency, particularly for hemophilia B, where treatment once weekly or every two weeks may be possible. Clinical trial of recombinant FIX fusion protein yielded mean half-life of 92 hours at the lowest dose (25 IU/kg) and after 14 days still had a 2.5% FIX level.

A key aspiration of hemophilia treatment is to allow patients to participate in normal activities and enjoy normal lives. A 2011 study on the correlation between annual number of joint bleeds and baseline FVIII activity level showed there is a crucial difference between 1% and 3% FVIII levels: patients with 3% FVIII level had only 1-2 joint bleeds per year. A 2017 study showed how EHL factor concentrates reduce infusion frequency, peaks and troughs, while gene therapy eliminates these burdens and provides higher and sustained factor activity levels, and could potentially cure the factor deficiency. Gene therapy must be initiated early in order to avoid joint disease, as pre-existing target joints will influence annualized bleeding rate.

Gene therapies will allow patients with hemophilia to aspire to and attain much better health outcomes and quality of life; this needs to be taken into account in defining the primary endpoints for clinical trials and clinical practice. In an ongoing study of BMN 270, a single-dose gene therapy for hemophilia A, all 7 patients in one cohort expressed FVIII levels above 50% and median and mean FVIII levels were sustained above 50% throughout 52 weeks of follow-up. The high dose cohort with 6 patients has shown that spontaneous bleeding stops with FVIII expression above 5%. The 50% FVIII levels achieved put patients within reach of the normal range of FVIII levels.

In a June 2017 editorial in *Haemophilia*, the World Federation of Hemophilia, European Haemophilia Consortium and National Hemophilia Foundation proposed that for gene therapy trials, clotting factor activity is a more accurate and objective primary endpoint to assess efficacy than annualized bleeding rate, with ABR and factor usage as important secondary endpoints.

Gene therapy for hemophilia A and B appears to be within a few years' reach and will potentially deliver a cure in the near future. Sustained FVIII and FIX levels above 10% have been achieved, with ABR dependent on joint status at the start of gene therapy. The primary outcome of gene therapy should be facotr levels sustained above 5%; health-related quality of life (HRQOL) depends on joint status at the start of gene therapy and socio-economic circumstances, and can be incorporated as secondary outcomes.

Gene therapy for hemophilia – the developing world

ALOK SRIVASTAVA, MD, CENTRE FOR STEM CELL RESEARCH, HEMATOLOGY DEPARTMENT, CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

The introduction of recombinant factor concentrates in the early 1990s was the most significant advance in hemophilia care since plasma-derived factor concentrates in the 1960s, and was heralded to lead to unlimited supplies and access around the world within 10-15 years. In reality, after 25 years, access to recombinant factor is still very limited in developing countries, with costs 2-3 times higher than plasma-derived factor. Today, with newer products coming into the market, i.e., extended half-life factor concentrates and novel bypassing agents, the expectation is for larger quantities of standard recombinant factor to become available in developing countries—but whether there will be such beneficial trickle-down effects remains to be seen.

Current gene therapy trials for hemophilia are mostly based on the AAV vector; there have been no major severe adverse events so far. A key challenge is AAV antibodies; it is estimated that 50% or more patients have significant anti-AAV neutralizing antibodies. There are several ongoing phase 1/2 trials which have all have shown good results, with factor levels ranging from 5% to 100%, and are moving towards phase 3 trial. A target of 5% factor level would bring dramatic improvements to people in developing countries with little or no access to treatment. There is a good chance that a hemophilia gene therapy will be ready and obtain market approval within two to three years, possibly in the form of a single-shot infusion that might well not even require hospital admission. However, the cost of approved vector-mediated gene therapy is in the range of US $375,000 to $475,000 per dose, which is prohibitively expensive for many parts of the world.

Investigation and development of an AAV-based gene therapy for hemophilia is being pursued by India's Centre for Stem Cell Research and Christian Medical College, in collaboration with U.S. researchers at Emory University and University of Florida. Strategies seek to improve factor expression by manipulating the AAV vector and transgene. The aims are to use an improved viral capsid (for more transgenes successfully delivered per viral particle), engineer better promoters (for more mRNA transcripts per transgene), apply a novel codon optimization strategy (for more FIX peptides per mRNA transcript), and bioengineer the FIX peptide for greater activity (more hemostatic efficacy per FIX peptide). Investigation is also underway of lentiviral vector-based transfer of FVIII cDNA into hematopoietic stem cells. Lentiviral vector-based gene therapy for hemophilia A offers a range of positives and negatives for young children in the developing world that need further examination. Positive advantages include long-term stable expression and safety of lentiviral vectors in hematopoietic stem cell; lentiviral vector-based gene therapy can be administered in very young children at 1-2 years of age. However, it is much more invasive administered through ex vivo transduction and autologous transplant of transduced cells, and there are safety concerns related to lentiviral vector integration as well as more production challenges.

A major hurdle for gene therapy is the regulatory aspect. Application for gene therapy clinical trial involves lengthy regulatory processes over numerous years, and extensive planning, meetings, and presentations to secure in principle approval of concepts and collaboration, submissions of data, and a detailed final protocol.

Efforts are also focused on increasing awareness and information among patient groups, through meetings with key leaders of the chapters of the Hemophilia Federation of India (HFI) in different cities in South India. Key objectives are to share information on gene therapy for hemophilia, develop protocol-specific documents for sharing with patients, and establish a robust consent process and long-term follow-up plans.

Discussion

Dr. Manuel Carcao noted that one of the "known knowns" according to Dr. Glenn Pierce is that gene therapy is not possible in young children, whereas Dr. Alok Srivastava described investigational lentiviral vector-based gene therapy that could potentially be administered at 1-2 years of age. There is also consideration as to whether AAV gene therapy would be possible in children around age 12—however, as Dr. Marijke van den Berg noted, a lot of the harm with hemophilia tends to occur earlier in life and once joint damage occurs, even if gene therapy is successful, the damage cannot be undone. Therefore, to be truly effective, therapy needs to be given much earlier. Is it definite and certain that AAV cannot be used in young children? Would it be possible to give young children AAV gene therapy with a goal of 5-10 years of factor expression, to be followed by gene therapy with a different AAV vector? Dr. Pierce said that studies show that neonatal mice did not achieve long-lasting expression from AAV gene therapy but it is unknown how this would translate in humans. By age 12, the liver is 70-80% of its full size, and most would agree that long-term expression would be possible if AAV gene therapy is given at age 12 or later. For young children ages 6-12, it could be possible to administer AAV gene therapy with the goal of 5-10 years of expression and then administer another gene therapy, possibly requiring a different vector serotype.

Dr. Carcao also noted that while patients who have ever had an inhibitor are currently excluded from hemophilia gene therapy, results to date suggest that gene therapy could play a role in prevention or eradication of inhibitors. Dr. David Lillicrap said that there are clinical examples where gene therapy in immune tolerance induction cases has reduced inhibitor level, and concurred that hemophilia patients with inhibitors is a population that could particularly benefit from gene therapy.

RESEARCH AND HEMOPHILIA TREATMENT

NEW AND NOVEL HEMOPHILIA THERAPIES: LATEST UPDATES FROM CLINICAL TRIALS

CHAIR: DAVID PAGE, WFH COAGULATION PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE CHAIR

At every WFH Global Forum, a session is dedicated to presentations and updates on novel technologies and new therapies for hemophilia and other rare bleeding disorders in the development pipeline. This session presented the latest clinical trial data from a lineup of novel and new gene therapies with the potential to advance treatment for hemophilia A and B patients with or without inhibitors.

Roche: Emicizumab prophylaxis – analyses from two phase 3 studies

MICHAEL CALLAGHAN, MD, CHILDREN'S HOSPITAL OF MICHIGAN, DETROIT, MICHIGAN, USA; CONSULTANT, ROCHE

Emicizumab (ACE910) is a novel therapy shown in clinical trials to be effective and provide substantially better results than existing treatments for patients with hemophilia A who develop inhibitors. It is a recombinant humanized bispecific monoclonal antibody that bridges activated FIX (FIXa) and FX to mimic the function of missing activated FVIII in hemophilia A patients. Once-weekly subcutaneous emicizumab prophylaxis has been shown to prevent or substantially reduce bleeds in children, adolescents, and adults with hemophilia A with inhibitors. Therefore, emicizumab could potentially be a new treatment option able to overcome current clinical challenges in hemophilia: the short-lasting effects of existing treatments resulting in the need for frequent venous access, and the development of FVIII inhibitors.

Dr. Michael Callaghan provided analyses from the Haven 1 and Haven 2 multicentre randomized phase 3 studies to evaluate the efficacy, pharmacokinetics, and safety of prophylaxis with emicizumab versus on-demand emicizumab therapy in adolescent and pediatric hemophilia A patients with inhibitors previously treated with bypassing agents. Most patients receiving emicizumab in Haven 1 and 2 have had zero bleeds, and emicizumab prophylaxis prevented or reduced bleeds in all bleed-related endpoints in both studies. Intra-individual comparison of 9 adolescent non-interventional study (NIS) patients in the Haven 1 study showed substantial reductions in treated bleed rates with emicizumab prophylaxis compared to prior prophylaxis with bypassing agents; 6 patients on emicizumab had zero bleeds (efficacy period 98–137 days). In the Haven 2 study, intra-individual comparison of 8 pediatric NIS patients receiving emicizumab showed all 8 patients had zero bleeds (efficacy period 85–99 days).

Haven 1 safety data showed that 78% of patients (25 of 32 adolescents) experienced at least 1 adverse event, with 62 adverse events in total; 2 patients had severe adverse events. In one case, a patient who had received repetitive doses of aPCC to treat a traumatic ankle joint bleed while on emicizumab prophylaxis developed thrombotic microangiopathy; aPCC was discontinued and TMA resolved, and the patient resumed emicizumab therapy. In Haven 2, 70% of patients (14 of 20 children) experienced at least 1 adverse event, with 41 adverse events in total. The most common adverse event was local mild injection site reaction; no patients tested positive for anti-emicizumab antibodies. There were 3 pediatric patients with serious adverse events, consisting of traumatic mouth hemorrhage, appendicitis, and catheter site infection.

Overall, emicizumab was demonstrated to have an acceptable safety profile; risk of TMA or thrombosis has been addressed through development of guidance on cautious use of concomitant bypassing agents. The data supports the potential for once-weekly subcutaneous emicizumab prophylaxis to provide a new standard of care for the management of adolescent and pediatric hemophilia A patients with inhibitors.

Spark: Overview of AAV-mediated gene transfer platforms for hemophilia A and B

MARCUS E. CARR, MD, PHD, HEAD OF CLINICAL DEVELOPMENT, SPARK THERAPEUTICS, PHILADELPHIA, PENNSYLVANIA, USA

Spark's gene therapies for hemophilia A and B use a recombinant adeno-associated viral vector (rAAV) for liver-directed FVIII/FIX gene transfer, selected for its enhanced safety due to its nonpathogenic and replication-defective characteristics. Since AAV is predominantly non-integrating, the risk of insertional oncogene activation is also substantially reduced.

A primary challenge of rAAV-mediated gene transfer is the potential development of dose-dependent capsid-specific T-cell immune response that limits efficacy, which has been reported in multiple trials. A phase 1/2 dose escalation clinical trial by Manno et al. in 2006 found that following infusion of a high dose of rAAV FIX into the hepatic artery, FIX activity initially increased but was halted and weakened by T-cell mediated response; a transient rise in liver transaminases fell back to normal levels without intervention, but was accompanied by a gradual decline in FIX activity back to pre-infusion, baseline levels. The results suggested that immunomodulation might be required to achieve long-term expression. In a 2011 clinical trial by Nathwani et al. of peripheral vein infusion of a self-complementary AAV vector with a serotype 8 capsid (scAAV8), the low-dose cohort did not experience significant AAV8-specific T-cell immune response; significant increases in T-cell immune responses occurred in the intermediate and high-dose cohorts but were mediated through administration of oral steroids as soon as a rise in alanine transaminase (ALT) was detected; transaminase levels then quickly returned to normal and residual FIX activity stabilized to provide continuing clinical benefit, with factor activity levels above 5%.

Spark's gene transfer therapies were developed based on the hypothesis that a highly efficient vector capsid and expression cassette, administered at low doses, will drive therapeutic levels of factor FVIII/FIX expression and minimize risk of a capsid immune response. Furthermore, no inhibitor development had been seen in all prior AAV liver-directed gene transfer clinical trials for hemophilia.

The investigational SPK-9001 vector was optimized to potentiate achievement of therapeutic goals at low dose ($5x10^{11}$vg/kg). The Phase 1/2a SPK-9001 trial is an open label, non-randomized dose escalation study of the safety and potential efficacy of SPK-9001 gene transfer in hemophilia B patients at least 18 years old, with baseline FIX activity levels of 2% or less, and previously treated for more than 50 exposure days. Patients were excluded if there was evidence or history of FIX inhibitor, liver fibrosis beyond stage 2, or active HBV or HCV. Patients with HIV were eligible as long as they were stable with CD4+ counts of at least 200/mm. Patients must exhibit a baseline phenotype with moderate to severe bleeding tendency as demonstrated by the need for prophylaxis, the occurrence of more than 4 bleeds per year, or evidence of severe arthropathy.

For the first 52 weeks, 8 patients achieved steady state FIX activity of about 30% and did not require steroids. T-cell immune response was monitored using the interferon-γ enzyme-linked immunospot (ELISpot) assay. Three patients had transient T-cell response that resolved without intervention. One patient had a capsid-directed immune response that was well controlled with prednisone, settling back to around 18% FIX activity level. Another patient with transaminase toxicity was given steroids starting on Day 36; immune response decreased and FIX activity of about 80% was sustained. The first 10 participants on SPK-9001 have shown 96% reduction in mean annualized bleed rate and 99% reduction in mean annualized infusion rate; 9 of these participants have not taken FIX concentrates to prevent or control bleeding events since vector administration. Participants have seen statistically significant improvement in quality of life from baseline as measured by health-related quality-of-life questionnaire.

Spark's gene therapy for hemophilia A, SPK-8011, is under investigation in a phase 1/2 dose escalation clinical trial. Three patients who received SPK-8011 so far show increased FVIII activity following gene

transfer, without any spontaneous bleeding episodes, safety issues, or serious adverse events to date. The first two patients given a single infusion at the lowest dose ($5x10^{11}$ vg/kg) showed a steady rise in FVIII activity that reached a stable plateau of around 11% and 14% of normal values at around 23 weeks and 12 weeks of follow-up. A third patient was then given a higher dose $1x10^{12}$ vg/kg); so far, this patient has had a greater increase in FVIII activity level than that observed in the first two patients, corresponding to the higher dose. No inhibitors to SPK-8011 have been detected and none of the patients have required steroid treatment.

Interim results from phase 1/2 AAV5-FVIII gene transfer in severe hemophilia A patients

BENJAMIN KIM, MD, BIOMARIN PHARMACEUTICAL INC., NOVATO, CALIFORNIA, USA

Dr. Benjamin Kim presented preliminary results from the first in-human study of BioMarin's gene transfer therapy called valoctocogene roxaparvovec (BMN 270) initiated in the U.K. in 2015. The ongoing phase 1/2 clinical trial recruited adults with severe hemophilia A (baseline FVIII level <1 IU/dL) previously on prophylaxis with FVIII concentrate or cryoprecipitate for at least 150 exposure days, or on-demand therapy for at least 12 bleeding episodes over the previous 12 months; and no history of inhibitors or no inhibitors in the past 12 months (<0.6 BU). Exclusion was based on detectable pre-existing AAV5 capsid immunity as measured by AAV5 transduction inhibition or AAV5 antibodies, HIV infectivity, and significant liver dysfunction (hepatitis B if positive surface antigen, hepatitis C if positive RNA). The trial endpoints are: safety of single intravenous administration of recombinant AAV5-FVIII vector; change in baseline FVIII activity level; and impact on frequency of FVIII therapy and annualized bleeding rate.

In total, 15 patients were enrolled sequentially in one of four cohorts. Gene transfer of AAV5-FVIII was administered in a single intravenous dose ($6x10^{12}$ vg/kg, i.e., 6E12 vg/kg, 2E13 vg/kg, 6E13 vg/kg, or 4E13 vg/kg). Dose escalation to the next cohort occurred if the resulting FVIII activity measured at 3 weeks was below 5 IU/dL. To date, valoctocogene roxaparvovec has been well tolerated across all doses. None of the patients have developed inhibitors. The most common adverse events across all dose cohorts were non-serious ALT elevation (10 patients, 67%), arthralgia (7 patients, 47%) and back pain, fatigue, or headache (5 patients each, 33%). Patients who received the highest dose (6E13 vg/kg) have sustained FVIII activity levels over 50% for more than 1 year after gene transfer therapy. Patients who received the 4E13 vg/kg dose had a slow and steady increase in FVIII activity, reaching normal range at 32 weeks post-infusion; patients in this dose cohort reduced mean annualized bleed rate by 92%, and mean annualized FVIII infusions by 97%. Breakthrough bleeding was averted with FVIII expression above 5%.

The 6E13 vg/kg cohort achieved a mean FVIII level of 104% and median FVIII level of 89% after 1 year, with 6 of the 7 patients sustaining above 50% FVIII activity. This dose has eliminated spontaneous bleeding and microbleeds, and provided FVIII coverage eliminating the need for FVIII even in cases of major trauma or surgery; except in 1 case involving a patient who required peri-operative FVIII infusions at endogenous FVIII level of 20 IU/dL. The 4E13 vg/kg dose was also associated with clinically meaningful efficacy, with slower but steady increase in FVIII activity approaching normal levels; this dose provided adequate FVIII coverage but additional on-demand FVIII would be needed in the event of surgery.

Overall, AAV5-FVIII gene transfer has been well tolerated to date; mild elevations in liver enzymes were transient and there are no significant qualitative differences between the 6E13 and 4E13 vg/kg dose cohorts and transient steroid use was well tolerated. Next, two phase 3 studies will be initiated with separate single arms (6E13 vg/kg and 4E13 vg/kg doses), to further study efficacy and clinically meaningful increases in FVIII in hemophilia A patients and AAV5-FVIII safety.

Alnylam Pharmaceuticals: Interim results from phase 2 extension study on fitusiran

PRATIMA CHOWDARY, MD, ROYAL FREE HOSPITAL HAEMOPHILIA CENTRE AND THROMBOSIS UNIT, LONDON, U.K.

Dr. Pratima Chowdary presented interim results from the phase 2 extension study of Alnylam's fitusiran, an investigational RNAi therapeutic targeting antithrombin for the treatment of hemophilia A or B patients with and without inhibitors. Fitusiran (ALN-AT3) is a subcutaneous small interfering RNA (siRNA) therapeutic targeting antithrombin. It is a non-biologic chemically synthesized drug with targeting ligand to specifically deliver to the liver, i.e., the site of antithrombin synthesis; and harnesses the natural RNA interference (RNAi) mechanism for regulation of plasma antithrombin levels. Based on the hypothesis that hemophilia A and B are characterized by ineffective clot formation due to insufficient thrombin generation, fitusiran is designed to lower antithrombin, with the goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding. A number of studies since 1993 have reported improved bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia, which has been supported by pre-clinical data from a 2015 study and emerging phase 1 clinical results reported this year.

The fitusiran phase 2 open-label extension study enrolled 33 patients previously dosed in the phase 1 study and eligible to roll over into the phase 2 study. Of 33 patients enrolled, 6 patients discontinued dosing: 4 discontinuations were due to withdrawal of consent; 1 due to an adverse event; and 1 due to a fatal severe adverse event. On September 1, 2017, dosing in the phase 2 study was suspended, due to the fatal event, with the remaining 27 patients potentially eligible to continue dosing once trial resumes.

Dr. Chowdary first presented safety results up until the date of transfer, June 15, 2017. Six patients had serious adverse events. Only 2 cases were considered possibly related to fitusiran; one patient had asymptomatic ALT and AST elevation which led to discontinuation and another patient with history of seizure disorder experienced seizure with confusion. About 70% of patients reported an adverse event; the majority of cases were mild or moderate in severity and unrelated to fitusiran. There were 6 patients with mild and transient injection site reactions (18%), 3 patients with abdominal pain (9%), 3 patients with diarrhea (9%), and 3 patients with headache (9%). ALT elevation was observed in 11 patients (all with HCV or past HCV infection); all cases were asymptomatic. Most cases were resolved (8 without dose interruption) with 1 last case in the process of being resolved. There have been no instances of drug-induced antibody formation. Overall, there have been encouraging results in patients with hemophilia A and B, with and without inhibitors. Once-monthly subcutaneous dosing achieved about 80% decrease in antithrombin with low inter-patient variability. Exploratory post-hoc analysis of bleed events found a median annualized bleed rate of 1 bleed; 16 patients (48%) were bleed-free and 22 patients (67%) have had no spontaneous bleeds.

In August 2017, a hemophilia A patient without inhibitors was admitted to hospital with a severe headache. A week prior to admission, he had experienced hip pain, treated with 3 doses of FVIII ranging from 31 to 46 IU/kg on 3 separate days; these doses were above the recommended range for mild or moderate bleeds per product label. The CT scan was read as subarachnoid hemorrhage, and the patient was treated with replacement factor therapy 2-3 times daily. However, his clinical course deteriorated and he subsequently had cerebral edema and died. The case was investigated by the hospital and reported as unrelated to fitusiran. Alnylam conducted further investigations including review of the patient's CT scans by three independent neuro-radiologists, who all confirmed on September 1, 2017, that the initiating event was cerebral venous sinus thrombosis, not subarachnoid hemorrhage. Alnylam elected to suspend fitusiran dosing in the clinical studies to further investigate the safety finding, now considered to be possibly related to fitusiran, and develop a risk mitigation plan with appropriate protocol amendments for enhanced patient safety monitoring. Study investigators and global regulatory authorities were notified. Alnylam announced that during this Global Forum, it reached alignment with the FDA on safety measures and a risk mitigation strategy to enable resumption of fitusiran dosing in the clinical studies.

uniQure: Interim results of phase 1/2 study of AAV5-FIX in adults with severe hemophilia B

EILEEN K. SAWYER, PHD, DIRECTOR, GLOBAL MEDICAL AFFAIRS, UNIQURE INC., AMSTERDAM, THE NETHERLANDS

Dr. Eileen Sawyer presented interim results from the phase 1/2 clinical trial of uniQure's AAV5 gene transfer therapy (AMT-060) in adults with severe or moderate-severe hemophilia B. AMT-060 uses the AAV5 capsid with wildtype FIX cassette, given the low prevalence of pre-existing anti-AAV5 antibodies in the general population. The international phase 1/2 study enrolled adults with severe hemophilia B (FIX activity below 1%) and adults with moderate-severe hemophilia B (FIX activity below 2%) on prophylactic FIX replacement therapy or on-demand FIX replacement therapy and severe bleeding phenotype (more than 4 bleeds per year, arthropathy). Exclusion was based on pre-existing neutralizing AAV5 antibodies (measured by a green fluorescent protein-based bioassay), FIX inhibitors, active HBV and/or HCV, or uncontrolled HIV (CD4+ ≤200/μL or viral load >200 gc/mL).

After each administration of AMT-060 to each patient, the Data Monitoring Committee evaluated available safety data over 24 hours before the dosing of the next patient could be initiated. Prophylactic FIX replacement therapy was tapered between weeks 6-12 if FIX activity was at least 2% for at least two consecutive follow-ups, and discontinued by 12 weeks if a minimum 2% FIX activity was maintained. The decision to continue tapering, and withhold, prophylactic FIX replacement therapy was based on individual assessment by the investigator, but included the requirement to document that the patient was able to maintain FIX activity level at 2% or more. Cohort 2 dosing was initiated after the completion of Cohort 1 dosing and review of initial safety data by the Data Monitoring Committee.

Nine of 10 patients were classified as severe hemophilia; 1 patient in Cohort 1 had a moderate/severe phenotype. Patients enrolled in Cohort 1 tended to be older and have more arthropathy and more bleeds in the year prior to study entry compared to Cohort 2, despite intensive prophylactic regimens. Stable dose-dependent increases in endogenous FIX activity were observed in both cohorts. Cohort 1 had mean FIX activity of 4.6% (range from 1.6% to 7.6%); Cohort 2 had mean FIX activity of 7.1% (range from 3.2% to 11.1%). As a result, 8 of 9 patients who were on prophylaxis at study entry discontinued prophylaxis. One patient in the low-dose cohort remained on prophylaxis with mean 1.3% endogenous FIX expression. There was a total decrease of 79% in cumulative annualized FIX consumption, from 2.64 million IU to 544,741 IU. Six patients (3 in each cohort) experienced treatment-related adverse events classified as possibly or probably related to AMT-060 (i.e., fever, asymptomatic liver enzyme elevation, pyrexia, anxiety, palpitations, headache, and rash). There were 14 treatment-related adverse events in total but none were classified as severe. ALT elevations were resolved with a tapering course of prednisolone without activation of capsid-specific T-cells or loss of FIX activity.

Blood samples retested for neutralizing activity with a novel highly sensitive luciferase-based assay detected 3 positive cases in the low-dose cohort; there was no correlation found between the neutralizing activity detected in vitro and clinical outcome. Transduction with AMT-060 was successful in patients with high-titer inhibitors; no patients with pre-existing inhibitors have developed inhibitors to AMT-060, as measured by luciferase assay, nor experienced ALT elevations.

Overall, patients have achieved and sustained increased FIX activity levels that have been stable and durable for up to 1.5 years of follow-up, including clinically relevant expression established in patients with pre-existing inhibitors. There have been no cases of inhibitor development, therefore, AMT-060 has potential as effective treatment for a broader patient population. A phase 3 study is planned for 2018, with the goal of optimizing FIX activity through incorporation of the Padua variant into the existing gene cassette, while preserving AMT-060's safety and utility characteristics (i.e., favorable safety profile, low immunogenicity, wide potential eligibility, predictable transgene expression, durability).

Bioverativ Therapeutics: Advancing the science of inhibitors

MAHA RADHAKRISHNAN, MD, SENIOR VICE PRESIDENT, MEDICAL, BIOVERATIV THERAPEUTICS, WALTHAM, MASSACHUSETTS, USA

The current gold standard for eradication of inhibitors to factor treatment is immune tolerance induction (ITI), which consists of long and intense treatment involving factor consumption up to 200 IU/kg daily for 10-48 months. ITI has around 70% success rate, however, there is a 30% relapse rate. The average cost for ITI treatment is around $1,463,688 per patient, with average treatment duration of 18.7 months. The average annual cost for prophylaxis with bypassing agents is $284,655 per patient.

A 2017 review study of inhibitor development in two maternal cousins with the same nonsense mutation, treated with similar intensity using either full-length FVIII or rFVIIIFc identified potential reasons for a lower anti-FVIII response in the patient treated with rFVIIIFc including: lower immunogenic potential of rFVIIIFc; genetic factors; environmental factors; and low concordance of inhibitor type even in inhibitor-prone families (72% in brothers, lower in cousins).

A 2016 study by Ragni et al. reported the development of a low-titer inhibitor in a child from an inhibitor-prone family, treated with rFVIIIFc before a first bleed, compared to a high-titer inhibitor in his maternal cousin with the same hemophilia A genotype, treated with recombinant FVIII before a first bleed. There was no anamnestic response, no requirement for port or ITI, and persistent and durable inhibitor suppression, despite continuing weekly rFVIIIFc prophylaxis. This was in contrast to the cousin who was treated with recombinant FVIII and developed a high-titer inhibitor, requiring ITI and port placement. Findings from this report of two cousins from an inhibitor-prone family history are consistent with the notion that rFVIIIFc may have tolerogenic properties in severe hemophilia A patients.

Three hemophilia A patients with inhibitors have had safe and successful ITI with rFVIIIFc (2 first-time ITI cases and 1 rescue ITI case), with rapid time to tolerization even when used at a lower dose frequency than conventional FVIII, including in a patient who previously failed ITI with another recombinant FVIII product.

A 2017 retrospective chart review by Carcao et al. assessed outcomes of ITI therapy with rFVIIIFc in patients with severe hemophilia A and high-titer inhibitors (7 first-time ITI cases and 12 rescue ITI cases) at 10 sites in the United States and Canada. Key findings include:

- rFVIIIFc led to rapid decrease in titers and rapid tolerization in first-time ITI patients with high-risk features.
- rFVIIIFc has therapeutic benefit as rescue therapy in patients who previously failed ITI.
- Higher dosing (≥130 IU/kg/day) led to rapid negative titer.
- There were no adverse events related to rFVIIIFc or with concomitant use of bypassing agents.

Given that rFVIIIFc may be less immunogenic and may induce rapid tolerance in inhibitor patients, two prospective phase 4 studies are now investigating the effect of rFVIIIFc in first-time ITI patients and in rescue ITI patients, i.e., hemophilia A patients with high-titer inhibitors (historical peak ≥5 BU) who have previously failed ITI. These studies are ongoing and recruiting across multiple hemophilia treatment centres in Canada, the United States, Europe, and Japan.

SAFETY RISKS DURING CLINICAL TRIALS: CAN THEY BE MINIMIZED?

CHAIRS: MARIJKE VAN DEN BERG, MD, WFH VP MEDICAL; GLENN PIERCE, MD, WFH MEDICAL ADVISORY BOARD MEMBER

In this session, safety data and experiences from clinical trials of novel bypassing agents were presented, along with perspectives and strategies on mitigation of safety risks with novel agents.

Safety data on emicizumab

GALLIA G. LEVY, MD, GENENTECH INC., SOUTH SAN FRANCISCO, CALIFORNIA, USA

Dr. Gallia Levy gave a comprehensive overview of the latest safety data from the Haven 1 clinical trial on emicizumab (ACE910). The Haven 1 clinical trial resulted in an 87% reduction in annualized bleed rate in adolescents and adults on emicizumab prophylaxis; 70% of patients previously on prophylaxis with bypassing agents achieved zero bleeds per year, and 62% of patients previously treated on demand with bypassing agents likewise achieved zero bleeds.

Most of the adverse events with emicizumab have occurred when patients were treated with bypassing agents for breakthrough bleeds or other reasons. No patients tested positive for anti-drug antibodies. The most common adverse event was local injection site reaction, experienced by about 15% of patients; 2 patients had adverse events leading to study withdrawal. About 8% of patients had serious adverse events; 3 patients had thrombotic microangiopathy (TMA), 2 patients had thrombotic events (TE), and there was 1 patient fatality. Following the occurrence of these serious adverse events, risk mitigation guidance were developed and implemented.

Both patients with thrombotic events recovered and restarted therapy. A patient with a traumatic joint bleed treated with activated prothrombin complex concentrate (aPCC) developed cavernous sinus thrombosis; he did not receive anti-coagulation and restarted emicizumab after MRI/MRV showed resolution of thrombosis; subsequently rFVIIa was used to treat traumatic joint bleeding, with no recurrence of thrombosis. The second case was a patient who treated two spontaneous bleeds with aPCC and developed skin necrosis and superficial thrombosis; he did not receive anti-coagulation and was treated with supportive care and wound debridement. Emicizumab was discontinued and there was no recurrence of thrombosis.

The three TMA events were unusual and unexpected. The first patient treated 2 joint bleeds with aPCC and experienced back pain; he was treated with rFVIIa and reported jaundice and weakness. He received therapeutic plasma exchange, with rFVIIa for central venous catheter placement, and the TMA was resolved. He subsequently had another joint bleed and received aPCC. There was no recurrence of TMA and emicizumab was discontinued. The second patient treated a traumatic joint bleed with aPCC and presented with emesis and mild abdominal pain. He received supportive care and the TMA was resolved with no recurrence. Emicizumab therapy was restarted. In both cases, TMA was resolved faster than classical TMA, which was associated with emicizumab in addition to aPCC treatment. The third patient suffered rectal hemorrhage on Day 237 and was treated with 11 doses of rFVIIa over 3 days; multiple interventions were unsuccessful at determining the source of the bleed. The patient received plasma exchange with albumin but refused blood transfusion; a large amount of aPCC was administered, well above the recommendation set out in the protocol guidance given the dire situation, which was further complicated by the refusal of blood transfusion, impeding any surgical intervention. The patient was given comfort care and died of rectal hemorrhage. The commonality among all cases was repeated doses of aPCC over multiple days prior to the event and improvement shortly after discontinuing aPCC, despite continued presence of emicizumab (due to its long half-life of 30 days). TMA events in two patients were short-lived and resolved soon after aPCC treatment was stopped; rFVIIa treatment in the first case included treatment during resolution of the event.

Analysis of cumulative aPCC dosing per 24-hour interval showed that 20 patients received aPCC for a total of 78 treatment episodes; 8 episodes involved average dose over 100 IU/kg/day, of which 5 were TE or TMA; and all TE/TMA events were seen in cases of cumulative doses of aPCC above 200 IU/kg for 24 hours or longer. Therefore, the risk was isolated to patients who received high doses of aPCC for multiple days. This is likely due to the presence of emicizumab substrates in aPCC, and accumulation of the substrates with repeated dosing; therefore, the same risk is not expected with rFVIIa. Further analysis of cumulative rFVIIa dosing found a wide variation, with some very large doses. Two patients had TMA events that were resolved soon after aPCC treatment was stopped. No TE/TMA events occurred in patients taking only rFVIIa, despite very high doses in some cases.

Following implementation of protocol changes specifying the avoidance of aPCC if possible, or use at lowest dose if necessary, there have been no further TE and TMA in over 150 patients with inhibitors and over 200 patients without inhibitors (the guidance was not followed in the case resulting in fatality due to the extenuating clinical circumstances). Therefore, risk of TE and TMA can be mitigated with clear guidance, particularly around the use of aPCC.

Bypassing agent dosing guidance for the treatment of breakthrough bleeds is currently under review by regulatory authorities and will be included in the label: "Unless no other treatment options are available, use of aPCC should be avoided. If aPCC is required in patients receiving emicizumab prophylaxis, the initial dose should not exceed 50 IU/kg. If bleeding is not controlled with the initial dose, the total aPCC dose should not exceed 100 IU/kg in the first 24 hours of treatment."

Fitusiran clinical development program overview and update

AKIN AKINC, PHD, ALNYLAM PHARMACEUTICALS, CAMBRIDGE, MASSACHUSETTS, USA

Dr. Akin Akinc gave an overview and update on Alnylam Pharmaceutical's ongoing development of fitusiran, an investigational RNAi therapy based on targeting antithrombin to improve thrombin generation. Antithrombin is a key natural anticoagulant protein that significantly decreases thrombin generation. It is produced by the liver and highly abundant in plasma. The therapeutic hypothesis is that lowering antithrombin levels in hemophilia patients will improve thrombin production and prevent breakthrough bleeding. Observation of improved bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia is supported by pre-clinical data and phase 1 clinical results. Therefore, this approach may be applicable for both hemophilia A and B, with or without inhibitors, and potentially other rare bleeding disorders.

Fitusiran is being investigated for the treatment of patients with hemophilia A and B, including those with inhibitors. It is administered subcutaneously, currently as a once-monthly dose. The phase 1 trial has been completed, with results consistent with the study hypothesis; a reduction in the antithrombin level by more than 75% from baseline resulted in increased thrombin generation, with median peak thrombin values at the lower end of the range observed in healthy individuals. Exploratory post-hoc analysis of bleed events showed a median of 1 annual bleed for all patients; about 48% of patients were bleed-free and 67% of patients had no breakthrough bleeds. The majority of adverse events were mild or moderate in severity. Fitusiran is to be further evaluated in phase 2/3 trials, however they were put on hold following a fatal serious adverse event that occurred after the date of data transfer—as a result, dosing in all fitusiran studies was temporarily suspended as of 1 September 2017.

The SAE mortality case involved a hemophilia A patient who had received on-demand therapy prior to the study and had an annualized bleed rate of 32. The patient received his first dose of fitusiran in late August 2015; after a gap, he enrolled in the phase 2 open-label extension trial in March 2016 and received 80 mg of fitusiran monthly. He was bleed-free since August 2016, for almost one year. In the week prior

to consulting a physician, the patient had exercise-induced hip pain and treated it with 3 doses of FVIII, ranging from 31 to 46 IU/kg, on three separate days; 5 days after initial treatment and 2 days before seeing a physician, he developed a severe headache, followed by vomiting. He then saw a physician and was admitted to hospital. Viral meningitis was suspected, therefore lumbar puncture was performed, with factor infusion before and after the procedure; results were negative. A CT scan was done and indicated subarachnoid hemorrhage. The patient was treated with standing replacement factor therapy 2-3 times daily to maintain FVIII trough levels of 43-50% and peak levels of 127-138% post-infusion. However, the patient's clinical course deteriorated with subsequent cerebral edema and death. The fatality was assessed by an investigator and deemed unrelated to fitusiran treatment, based on reports from the treating hospital.

Alnylam initiated further investigations including review of the patient's CT scans by three independent neuro-radiologists, who all confirmed on September 1, 2017, that the initiating event was cerebral venous sinus thrombosis, not subarachnoid hemorrhage; therefore, it was now deemed to be possibly related to the study drug. Alnylam elected to temporarily suspend dosing in fitusiran studies to further investigate this safety finding and to develop a risk mitigation plan; the company also notified study investigators and global regulatory authorities. Alnylam has since examined its protocols and consulted experts on possible measures for risk mitigation. No definitive conclusions can be drawn; however, the sequence of events suggest that the use of full-dose factor in combination with fitusiran may have contributed to initial development of thrombosis in the patient.

Alignment was reached with the FDA on new clinical risk mitigation measures that include: updated bleed management guidance for investigators and patients to use reduced doses of factor/bypassing agent while on fitusiran given emerging data suggesting that lower than typical doses may be effective in bleed management in the setting of fitusiran; and enhanced patient safety monitoring for thrombosis. Alnylam is now submitting amended protocols and other trial materials to regulatory authorities, with the aim to reinitiate dosing in clinical studies around year-end, subject to approval of regulatory authorities.

Assessing pro-coagulant and anti-coagulant pathways in patients treated with new agents

KENNETH MANN, MD, PROFESSOR AND CHAIR OF BIOCHEMISTRY, UNIVERSITY OF VERMONT, USA

Dr. Kenneth Mann began with an overview of the hemostatic process following exposure of tissue factor to blood. Initiation of coagulation and thrombin generation begins with tissue factor binding to activated FVII, which triggers a cascade of reactions including the activation of FIX, FX, prothrombin, platelets, FXIII, FV, and FVIII. The FVIIIa/FIXa complex amplifies propagation of FXa, which then combines with FVa to form the prothrombinase complex, which converts prothrombin to thrombin. During the initiation and propagation phases, procoagulant activity is suppressed by anti-thrombin III and tissue factor pathway inhibitor (TFPI) or inactivation of FVa and FVIIa by activated protein C. The thrombin activates FXIII and fibrin resulting in clot formation. In hemophilia, the FVIII/FIX deficiency impedes formation of the FVIIIa/FIXa complex, amplification of FXa generation, and correction of the bleeding problem.

A study of thrombin generation in whole blood involving 13 healthy individuals found consistent individual thrombin production but significant variation from individual to individual in thrombin levels and hemostatic response. Historical data from individuals with severe hemophilia showed a 5- to 7-fold variation in ability to generate thrombin; the highest levels of thrombin in hemophilia patients fell within the normal healthy range, while low thrombin levels were associated with longer time to clot (reach 10 nm thrombin). Computer evaluations suggested that actual human individuals characterized by an International Normalized Ratio (INR) of 1 ± 0.1 may have quite different thrombin generation; while when assessed by prothrombin time these individual responses are indistinguishable (INR = 1 ± 0.1). Similarly, numerical models

evaluating hypothetical individuals with hemophilia A whose plasma factor levels might correspond to otherwise high or low "healthy" ranges produced dramatically different thrombin generation results.

A number of studies have examined the correlation of thrombin generation to severe hemophilia phenotype. A 2007 study at the Van Creveld Clinic found thrombin generation levels were similar among patients with different phenotypes of severe hemophilia. However, a 2006 Italian study found thrombin generation appeared to predict clinical phenotype in severe hemophilia patients. Meanwhile, a 2009 study showed that the presence of corn trypsin inhibitor is predictive of bleeding risk in hemophilia A.

While early hemophilia treatments were based on pro-coagulant strategies, current approaches under investigation include strategies based on decreasing inhibition of coagulation and bypassing FVIII/FIX, and analysis of patient plasma composition to estimate individual thrombin generation potential. Better assessment tools are needed for hemophilia therapies, including factor replacement therapy.

Discussion

This critical session underlined earlier discussions at this Global Forum on the relevance of real-world clinical data and capturing what happens in the real world outside the controlled setting, said Dr. Lydia Abad Franch of Shire. When assessing serious adverse events, particularly TMAs, it is important to know whether an event is the effect of interaction between different drugs. Industry needs to take these lessons into account when designing clinical trials for the market; manufacturers need to pay careful attention and provide concise guidance to physicians and patients on drug interaction risks and how to mitigate and avoid risk of thrombotic events and TMA.

David Page, chair of the WFH Coagulation Product Safety, Supply and Access Committee, noted that treatment protocols are currently being revised and encouraged the manufacturers to consult with the WFH on development and rollout of revised protocols to ensure that patients understand the new protocols and abide by them. It is also important to understand the implications for dentistry and disseminate information and guidelines for dental procedures, said Dr. Andrew Brewer, member of the WFH Dental Committee. Both manufacturers reported that dental procedures including dental extraction have been done without the use of additional factor product.

Dr. Alok Srivastava noted that Dr. Kenneth Mann described the individual to individual variations in thrombin levels and hemostatic response, while Dr. Akin Akinc and Dr. Gallia Levy both reported cases of breakthrough bleeding. It would be useful to have a post-marketing surveillance strategy for the occurrence of hemostasis issues and breakthrough bleeds, along with clear guidelines to ensure that patients get appropriate treatment as soon as possible. Dr. Glenn Pierce added that there are patients who self-treat with bypassing agents without medical supervision, therefore it is critical to educate patients to consult their physician immediately if they have breakthrough bleeding to determine how to treat it. Physicians should likewise be informed, and treatment and dosing information should be included on the patient's medical card for emergency situations.

UPDATE ON PLASMA-DERIVED PRODUCT RISKS

CHAIR: MAGDY EL EKIABY, BLOOD TRANSFUSION AND HEMOPHILIA TREATMENT CENTRES, SHABRAWISHI HOSPITAL, CAIRO, EGYPT

About 75% of people with hemophilia worldwide lack access to treatment with factor concentrates. Although recombinant factor concentrates have become standard treatment in many developed countries and extended half-life factor products and novel technologies offer even more advanced therapy, plasma-derived factor concentrates remain in many cases the best option available in developing countries. Ensuring the highest levels of safety against existing and emerging pathogens is critical.

Overview of the safety margins of current plasma-derived factor concentrates

THOMAS R. KREIL, PHD, SENIOR DIRECTOR, GLOBAL PATHOGEN SAFETY, SHIRE PHARMACEUTICALS

Safety of plasma-derived factor concentrates relies on robust viral reduction and inactivation measures that are built into manufacturing processes and critical to maintaining the very high safety of plasma products today, said Dr. Thomas Kreil. Still, continual vigilance is essential; it is important to investigate all newly emerging bloodborne pathogens, verify the underlying assumptions, and confirm that the viral reduction methods used in manufacturing are effective against the new threat.

To ensure the highest levels of safety in the blood supply and blood products for transfusion, vigorous blood screening for infectious viruses is absolutely critical as it is the only means for viral reduction and removal. Current viral detection technologies are highly effective. Multiplex polymerase chain reaction (PCR) testing and immunological assays are typically used to test blood samples for HIV, HBV, HCV, HAV, and B19 viruses, and in recent years, emerging pathogens such as West Nile Virus (WNV), and HEV. The same robust test methods are applied to plasma for fractionation, through mini-pool testing for HIV, HBV, HCV, HAV, and B19, followed by re-testing of the manufacturing plasma pool. In reality, it is arguable that plasma testing is a redundant safety measure because the safety of plasma-derived products ultimately and wholly depends on the viral inactivation and removal steps embedded in the manufacturing process. Hence while blood screening has incorporated WNV and HEV assays, this has not been done in plasma screening because of the substantial virus reduction measures already in place, which provide exponentially superior safety margins. Donor selection and blood testing each have a 100-fold risk reduction capacity, but testing is limited to known pathogens—whereas safety measures in manufacturing have 1 million-fold risk reduction capacity, due to robust steps for generic removal of impurities followed by viral inactivation.

Over the past two decades, health authorities and the blood and plasma industry have confronted a number of new and emerging bloodborne pathogens presenting serious harmful risks to human health globally including WNV, H5N1 influenza, Chikungunya virus (CHIKV), HEV, and Zika virus (ZIKV). All of the viruses were met with rapid response and investigated; the underlying assumptions were confirmed to be valid and viral inactivation measures were shown to effectively remove the pathogens. It is important to note that WNV, H5N1, CHIKV, HEV, and ZIKV are all lipid-enveloped viruses and there is historic evidence that current viral inactivation technologies such as nanofiltration and solvent detergent are very effective; these assumptions are extrapolated to new unknown pathogens identified to be lipid-enveloped viruses.

HEV is prevalent around the world and particularly widespread in Asia and underdeveloped countries, where transmission via drinking water contamination is common; China has developed an HEV vaccine, recently licensed and exclusively available there. There have been some rare cases of HEV transmission via blood transfusion, and the occasional detection of HEV RNA in plasma pools indicates that HEV viremic donations might enter the manufacturing process of plasma products. HEV is a complex nonenveloped virus within a lipid envelope, i.e., lipid-enveloped nonenveloped virus.

In 2015, the European Medicines Agency conducted an extensive review of plasma product safety vis-à-vis HEV and concluded: "Robust inactivation/removal of HEV is the key factor towards the HEV safety of plasma-derived medicinal products and manufacturers are advised to assure that their manufacturing processes are effective against HEV. Equally it is recognized that extrapolation of virus reduction data from model viruses for HEV might be difficult in several cases." To verify the safety margins of plasma products with respect to HEV, virus reduction steps commonly used in manufacturing processes were investigated for their effectiveness against HEV. Substantial HEV reduction was confirmed in the processes commonly used in the production of plasma products: FVIII (immunoaffinity purification, 20-nm nanofiltration), immunoglobulin (cold ethanol fractionation, 35-nm nanofiltration, low pH), albumin (heat treatment), and aPCC (35-nm nanofiltration, heat treatment).

Thus there is considerable evidence that manufacturing processes are effective against lipid-enveloped viruses and would be capable of confronting new emerging lipid-enveloped viruses. However, non-lipid enveloped viruses still require vigilance and verification to ensure that safety margins are maintained.

Viral-inactivated cryoprecipitate: A global initiative

JEAN CLAUDE FABER, PRESIDENT, ASSOCIATION LUXEMBOURGEOISE DES HÉMOPHILES

Despite the longtime availability and standard use of factor concentrates for hemophilia treatment in the developed world, and diverse efforts by national and international organizations over the past 30 years to advance access to treatment, cost remains a barrier in developing countries and the majority of people with hemophilia today still have stark or inadequate treatment, said Jean Claude Faber. The experience has shown that hemophilia treatment approaches based solely on factor concentrates cannot solve the needs in countries with limited resources.

Improvements to blood systems and blood centres in many developing countries in recent years and the introduction of novel technologies for viral inactivation of blood components have presented new avenues for progress. Several developing countries have introduced local preparation of virally inactivated cryoprecipitate, which has proven to be safe and effective treatment for patients with bleeding disorders and is an affordable and viable treatment option in the developing world. Almost all countries have blood collection and systems for separating whole blood donations into blood components; thus they have the capacity to produce safe cryoprecipitate by incorporating just one additional viral inactivation step to processes at existing blood centres.

Viral inactivation technologies for plasma and platelets include the newly licensed Intercept® system by Cerus based on amotosalen and ultraviolet A illumination, and the Mirasol® system by TerumoBCT based on riboflavin and ultraviolet light; both are moving through validation and market authorization for cryoprecipitate. Current options for viral inactivation of cryoprecipitate include the CRYO-SD/F® system by VIPS based on solvent detergent and filtration, which has been available since 2010.

Given the long-existing challenges of inadequate factor supply and availability in developing countries, the Luxembourg Hemophilia Association launched a global initiative in 2016 to promote local preparation of viral-inactivated cryoprecipitate in developing countries, to facilitate implementation of an alternative strategy to make available sustainable and affordable treatment for hemophilia and other bleeding disorders. The primary goals are to work with national and international stakeholders on six core interventions including: revise and update standards and guidelines on hemophilia treatment to include virally inactivated cryoprecipitate; advocate for local preparation of safe cryoprecipitate in developing countries; implement a pilot implementation program; and establish a program to implement local cryoprecipitate production in developing countries. Collaboration with international bodies and national stakeholders (i.e., health and regulatory authorities, national blood services, medical experts, patient organizations) in developing countries is key.

Cryoprecipitate standards and guidelines should allow tailoring to specific country situations (e.g., dual sets of products and doses), conform with policies and strategies for hemophilia treatment with other therapies, and be updated regularly to keep up with rapid advances in science and manufacturing processes. Guidelines should also include pragmatic stratification according to:

- countries (given considerable differences between developed and developing countries, a single set of principles cannot serve all patients adequately);
- patients (i.e., inherited bleeding disorders such as hemophilia, VWD, and fibrinogen abnormalities as well as acquired bleeding disorders such as fibrinogen consumption/depletion in childbirth resulting in impaired hemostasis and increased maternal mortality);
- products (clotting factor concentrates and other hemostatic products, including viral-inactivated blood components such as cryoprecipitate);
- sub-classes of medicinal products (plasma-derived and recombinant factor; full-length, B-domain deleted and fusion clotting factors);
- treatment protocols (prophylaxis, on-demand regimens);
- dosage (high, intermediate, and low-dose regimens);
- care delivery (home treatment/self-infusion, hospital/clinic, etc.).

The International Society of Blood Transfusion, World Health Organization, and World Federation of Hemophilia are currently independently in the process of guidelines review and revision, which will incorporate virally inactivated cryoprecipitate.

Moving forward, a key priority is collaboration with national patient organizations and the WFH on effective advocacy for local preparation of cryoprecipitate in developing countries, including discussion with health authorities and other national stakeholders on important issues related to hemophilia treatment (safety, complications, quality, supply, availability, access, affordability, direct and indirect costs, etc.). With staff and equipment already in place at blood centres, the pilot project will involve training and education of blood centre staff on viral inactivation devices and clinicians on cryoprecipitate usage and implementation of quality management and workflows. A number of pilot sites have been recruited and funding has been secured for the pilot phase.

WFH RESEARCH: CLINICAL RESEARCH GRANT PROGRAM

CHAIR: DAVID LILLICRAP, MD, WFH CLINICAL RESEARCH GRANT REVIEW COMMITTEE CHAIR

The WFH Clinical Research Grant Program supports clinical research projects that have the potential to influence the care of inherited bleeding disorder populations and encourage international collaborative research initiatives. Four clinical research grants were awarded in 2017.

Prevalence of mild FXIII deficiency in the German population and potential clinical impact

SNEHA SINGH, MD, INSTITUTE OF EXPERIMENTAL HAEMATOLOGY & TRANSFUSION MEDICINE, UNIVERSITY OF BONN, GERMANY

Dr. Sneha Singh gave an overview of recent understanding and research on mild FXIII deficiency caused by heterozygous mutations, including research on its prevalence in the German Caucasian population and potential clinical impact, on behalf of Dr. Arijit Biswas, recipient of a WFH clinical research grant in 2016. FXIII is the terminal player in the coagulation pathway. It circulates in plasma and, upon activation by a combination of thrombin cleavage and calcium binding, crosslinks pre-formed fibrin clots to protect them from premature fibrinolysis. Severe FXIII deficiency is an autosomal recessive genetic disorder that occurs in 1 in 4 million people and results in bleeding problems. Bleeding symptoms can be mild, moderate or severe. Common severe symptoms include umbilical cord bleeding, nosebleed, easy bruising, joint bleeding, bleeding in the mouth and gums, and bleeding in the central nervous system.

Mild FXIII deficiency has largely been neglected because clot solubility assays only pick up FXIII activity below 3%; therefore, they only detect the severe form. FXIII levels above 10% are adequate to prevent spontaneous bleeding. Mild FXIII deficiency is attributed to the complex structure of FXIII; even a single mutation of any of two subunits gives rise to at least 75% defectivity and while there should remain sufficient FXIII to provide the 10% activity level necessary to avert bleeding symptoms, some mild carriers experience bleeding symptoms. Thus there is large individual variability in circulating plasma FXIII levels (65-150%).

Dr. Singh described an ongoing study that involves screening and analysis of F13B gene defects in the German population. So far, 852 blood samples have been collected from apparently healthy controls; the target data set is 1,000. Two types of studies are being done. The plasma study consists of blood sample collection, plasma separation, and evaluation of FXIII activity level, FXIII rate of activation, FXIII antigenicity, alpha-2-antiplasmin incorporation and plasma fibrinogen levels, VWF, prothrombin time, and activated partial thromboplastin time (APTT). So far, 592 blood samples have been analysed for mild FXIII deficiency (20-80% FXIII level); 29 cases of mild FXIII deficiency have been identified, 48% of which are easy bleeders with a tendency for nosebleeds and hematomas. Plasma analyses have also found substantial variation in rate of activation. The genomic DNA extraction study involves next generation sequencing for the F13A1, F13B, FGN genes and other genes involved in coagulation cascade. So far, analysis of genetic data from 6 individuals suggests that genetic variants and polymorphisms identified in the F13A1 gene are associated with low FXIII activity levels and mild FXIII deficiency. These studies will be followed by final assimilation of results using statistical and functional analyses to determine the prevalence of mild FXIII deficiency in the German Caucasian population, its correlation to the genotype, and its clinical relevance and impact.

Investigators are now completing next generation sequencing of the remaining patients with mild FXIII deficiency (20-80%) and a comparative cohort of about 300 patients selected from the remaining pool (at least 80% FXIII activity). Work is also ongoing on antigenic profiling of all samples to check activity–antigen correlations and an alpha-2-antiplasmin incorporation assay to compare and correlate variability in activity observed in the collected cohort. A final statistical and functional evaluation including haplotype and logistic regression analyses will be done after completion of the laboratory and clinic work.

In mild cases of FXIII deficiency, heterozygous mutations and background polymorphisms (intronic or coding) in combination can affect aspects of the tetramer assembly or disassembly/dissociation, thereby resulting in variability in FXIII activity levels among individuals. Mild FXIII deficiency cannot be viewed in isolation as a distinct entity linked to only one variant. While heterozygous missense variants do occur frequently, the net phenotype of mild FXIII deficiency depend on other factors; possible genetic factors include fibrinogen levels and untranslated region (UTR) polymorphisms affecting levels of FXIII in small dosages. Several of the coding heterozygous variants that so far have been classified as polymorphisms based on their prevalence might in fact affect subtle functional aspects such as the rate of FXIII activation or interaction between the A and B subunits, thereby resulting in individual-specific phenotype.

ELISA-based VWF functional screening assay for discriminating phenotypic variants of VWD

JONATHAN C. ROBERTS, MD, BLEEDING AND CLOTTING DISORDERS INSTITUTE, PEORIA, USA

Von Willebrand disease is considered the most common inherited bleeding disorder but is also very difficult to diagnose. Laboratory diagnosis requires a series of assays of von Willebrand factor quantity and function as well as FVIII activity, and assessment of VWF–platelet interactions and VWF–FVIII interactions; there is currently no single straightforward diagnostic test available to either confirm or exclude diagnosis. Dr. Jonathan Roberts, recipient of a 2015 WFH clinical research grant, presented his research and development of a new VWD phenotyping assay which has potential to refine laboratory diagnosis of VWD and have widespread applicability.

The VWF multiplex activity assay is based on the enzyme-linked immunosorbent assay (ELISA) and linear discriminate analysis using a statistical algorithm for variant VWD phenotype assignments. The assay measures various activities of VWF on a single plate: VWF antigen, platelet glycoprotein Ibα (GpIbα) binding to VWF, VWF–FVIII binding, VWF–collagen 3 binding, and VWF propeptide. Additional VWF activities can be added. The assay was used to evaluate 160 samples of patients with type 2 VWD enrolled in the Zimmerman Program for the Molecular and Clinical Biology of von Willebrand Disease. The algorithm for linear discrimination accurately identified variant VWD phenotype (type 1C, 2A, 2B, 2M, or 2N VWD) in 92.5% of cases (124 of 134 patients). Cross-validation using the Jackknife statistical resampling technique, which predicts assay application to a general population, showed that the linear discriminant algorithm correctly assigned variant VWD phenotype in 88.1% of cases (118 of 134 patients).

In addition, the VWF multiplex activity assay demonstrated correlation with traditional clinical laboratory VWF assays. Comparative analysis was performed on all available clinical data for the study cohort with clinical data from the Zimmerman Program. Evaluation of all phenotypic variants of VWD in all VWD patients demonstrated at least 80% correlation to the routine clinical assay in most cases.

Prospective investigation of the assay is underway as part of a comparative effectiveness study on VWD diagnosis in individuals undergoing evaluation for a clinical bleeding disorder at the Bleeding and Clotting Disorders Institute, in collaboration with hematologists Robert Montgomery and Thomas Abshire. The study population includes people with all types of VWD, low VWF, and normal subjects. The goal is to enroll 600 individuals with VWD over 4 years.

To data, samples from 126 blinded subjects have been evaluated on the VWF multiplex activity assay; analysis of the preliminary data is ongoing and more blinded subjects are in process of evaluation. Data will be correlated to confirmed VWD phenotype from the Zimmerman VWD RO1 Study. Following full patient enrollment, there will be evaluation of the complete VWD cohort from the Zimmerman VWD RO1 Study, followed by sub-analysis to determine the VWF multiplex activity assay's ability to discriminate low VWF from type 1 VWD and normal subjects.

WFH DATA COLLECTION PROGRAMS

CHAIR: ALAIN BAUMANN, CEO AND EXECUTIVE DIRECTOR, WORLD FEDERATION OF HEMOPHILIA

This session presented two WFH data collection programs: the Annual Global Survey (AGS) and the World Bleeding Disorders Registry (WBDR). The AGS gathers selected national demographic and treatment data on people with hemophilia and other inherited bleeding disorders throughout the world. The WBDR is a newly developed web-based, patient registry that provides a platform for a network of hemophilia treatment centres to collect uniform and standardized data on people with hemophilia. These two programs collect important information that is used to support efforts to improve bleeding disorders treatment and assist with program planning.

Annual Global Survey

DONNA COFFIN, MSC, DIRECTOR, RESEARCH AND PUBLIC POLICY, WORLD FEDERATION OF HEMOPHILIA

The WFH Annual Global Survey is a cross-sectional survey sent to national member organizations (NMOs) every year, for a global overview of the state of treatment and access to care for people with hemophilia and other bleeding disorders throughout the world. The survey gathers country-level data on the number of identified patients by type of hereditary bleeding disorder (including hemophilia, von Willebrand disease, factor deficiencies and platelet disorders), gender and age of patients, as well as data on availability, usage and cost of factor concentrates and other treatment products. The AGS includes country-level, aggregate data collected through national registries or the NMOs, whereas the WBDR is a patient registry that consists of patient-level, de-identified data collected through HTCs.

The 2016 Report on the Annual Global Survey represents data from 113 countries. In total, 295,866 people with hereditary bleeding disorders were identified worldwide: 184,723 people with hemophilia (149,764 hemophilia A and 29,712 hemophilia B), 71,648 people with von Willebrand disease, and 39,495 people with other rare bleeding disorders. The median global per capita FVIII usage was 0.83 IU per capita, with a range of 0.07 to 4.18 IU per capita.

The annual data is used to measure the success of WFH programs such as the Humanitarian Aid Program, Global Alliance for Progress (GAP), Cornerstone Initiative, regional workshops, and data collection workshops—and provide the underpinning for evidence-based advocacy. Per capita factor usage is used to track progress in individual countries and globally. With the expansion of the Humanitarian Aid Program in 2015, the volume of donated products has increased substantially and the data shows the number of patients identified has increased alongside. In 2016, the reported per capita factor use initiates a differentiation between purchased factor concentrates and donated factor concentrates (i.e., humanitarian aid). In Africa, most reporting countries fall within the low and lower-middle income categories in terms of gross national income (GNI) and many rely on humanitarian aid for hemophilia treatment, with factor use far below the minimum standard of 1 IU per capita; only Mauritius and South Africa, both in the upper-middle income GNI category, purchase large quantities of factor, with 1.753 IU of FVIII per capita and 1.049 IU FVIII per capita purchased respectively in 2016.

In terms of global hemophilia care, the 184,723 people with hemophilia identified in 2016 represent approximately 40% of the estimated 450,000 people with hemophilia expected worldwide, based on current prevalence estimates, of which an estimated 30% have access to adequate care. Therefore, it is evident that much work still needs to be done to improve the availability of treatment and access to care, particularly in developing countries.

Launch of World Bleeding Disorders Registry

GLENN PIERCE, MD, PHD, CHAIR, WORLD BLEEDING DISORDERS REGISTRY STEERING COMMITTEE

Dr. Glenn Pierce gave an overview of the WFH World Bleeding Disorders Registry to be rolled out at the end of 2017. The implementation of the WBDR follows 2 years of development by an expert steering committee, and successful completion of a pilot study conducted in 25 countries (April to December 2016), which demonstrated the feasibility of conducting a global patient registry across countries with varying levels of care. The WBDR database is being developed through a collaboration of WFH, Sweden's Karolinska Institute, and Health Solutions.

Global involvement of HTCs, NMOs, and patients is vital to the success of the registry. The enrollment targets for the first 5 years are to enroll 200 HTCs, representing 50 countries, and 10,000 patients with hemophilia. Enrolment will begin in the next few months, with information letters being sent to NMOs and invitations to HTCs.

The WBDR Steering Committee is developing a data linkage strategy for countries that have established patient registries, such as Canada, United States, France, the U.K., Italy, Sweden, and others. A data management plan with built-in data validation and review processes is also under development. A WBDR training program will include online and in-person training, and resources such as user manuals, online tutorials, and web seminars.

HTCs will have access to their own centre's data only and will be able to use the WBDR platform to track and follow patient progress. HTCs within a country will have the ability to pool their data for country-wide data, through a Data Sharing Agreement. Participating HTCs will be able to submit research questions to the WBDR Research Committee. The minimal data set will be implemented first, which includes the collection of demographic data (gender, date of birth, country of residence), disease history data and diagnostic data; and prospectively collected data at each HTC follow-up visit (bleeding events, target joints, treatments, inhibitor assessment, hospitalization, and mortality). There will be ongoing safety surveillance of the minimal data set and safety outcomes, i.e., inhibitor status, hospitalization, and mortality.

The WFH World Bleeding Disorders Registry is supported by funding from Shire, SOBI, Bayer, Grifols, Pfizer, Roche and Sanofi.

CONCLUSION

WFH Executive Director Alain Baumann thanked the international experts who contributed invaluable knowledge and time towards planning the 10th WFH Global Forum: David Page, WFH Coagulation Product Safety, Supply and Access Committee Chair; Dr. David Lillicrap, WFH Clinical Research Grant Review Committee Chair; Dr. Marijke van den Berg, WFH Vice President Medical; Dr. Glenn Pierce, WFH World Bleeding Disorders Registry Steering Committee Chair; and WFH Research and Public Policy Director Donna Coffin, Senior Public Policy Officer Mark Brooker, Senior Congress and Meetings Manager Hélène Lussier, and Congress and Meetings Manager Emilie Réhel.

In closing, he thanked the sponsors who provided vital financial support for the 2017 WFH Global Forum: Bayer, Platinum Sponsor; and Gold Sponsors – Alnylam Pharmaceuticals, BioMarin, Sanofi Genzyme, Héma-Québec, Novo Nordisk, Roche, and Spark Therapeutics.

APPENDIX: GLOBAL FORUM AUDIENCE POLL RESULTS

1. Compared to standard half-life factor concentrates, and based on available evidence, what is the biggest benefit of extended half-life factor concentrates?

Fewer bleeds	3%
Better adherence to prophylaxis	9.1%
Improved quality of life	12.1%
All of the above	72.7%
None of the above	3.0%

2. Are we prepared to make the case to health systems to pay for gene therapy?

Yes	22.7%
Somewhat	25.3%
No	37.3%
I don't know	14.7%

3. Which variable will be the most important determinant of value of gene therapy?

Projected cost savings over a patient's lifetime	18.2%
Sustainability of improved factor level (how long it lasts)	21.8%
Degree of health improvement (factor level achieved)	23.6%
Outcomes relative to cost	36.4%

4. From your perspective, do you believe patients…

Want to be cured	34.3%
Need to be cured	14.3%
Both	42.9%
Neither, treatment is adequate now	8.9%

5. What is a cure worth?

US$20,000,000	10.9%
US$1,000,000	8.7%
US$100,000	10.9%
US$10,000	2.2%
Price parity with one year's treatment cost	6.5%
Price parity with two years' treatment cost	15.2%
Price parity with three years' treatment cost	45.7%

6. Will gene therapy be affordable outside of highly developed countries?

Yes, low resource countries will see value in introducing gene therapy today, even though they do not currently provide for optimal hemophilia treatment	8.6%
Yes, but only if there is significant differential pricing	32.1%
No, at least for the foreseeable future	24.7%
No, even highly developed countries will have trouble affording it	29.6%
No opinion	4.9%

7. Current treatment of hemophilia is considered to be safe and effective. With regard to this statement, do you…

Agree fully	30.6%
Agree mostly	54.8%
Not sure	11.3%
Disagree mostly	1.6%
Disagree fully	1.6%

8. In a chronic disease, will you call 'effective' and 'safe' a treatment which does not allow the patient to live a completely normal life and can lead to serious adverse effects in 20-30% of patients?

Definitely no	43.4%
Perhaps no	41.5%
Not sure	1.9%
Perhaps yes	9.4%
Definitely yes	3.8%

9. The main reason for ineffectiveness of current hemophilia therapy is the low trough level with current therapies. With the current options of therapy, including those in clinical trials, what trough level will you recommend for most patients?

>5%	20.3%
>15%	35.9%
>30%	20.3%
>50%	17.2%
>100%	6.3%

10. Current treatment of hemophilia is neither safe (20-30% inhibitors) nor effective (breakthrough bleeds and restrictions on activities). With regards to this statement, do you…

Agree fully	20.8%
Agree mostly	25.0%
Not sure	12.5%
Disagree mostly	37.5%
Disagree fully	4.2%

11. With regards to clotting factor replacement therapy, including extended half-life products, what trough level will you recommend?

>3%	12.3%
>5%	31.5%
>10%	12.3%
>15%	23.3%
>30%	20.5%

12. With regards to gene therapy for hemophilia, what factor level will you consider to be an acceptable outcome for regulatory approval of the therapy?

>5%	11.4%
>10%	11.4%
>15%	13.6%
>30%	34.1%
>50%	29.5%

13. With regards to therapy with non-clotting factor hemostatic drugs, what trough level will you recommend?

>5%	12.5%
>10%	16.1%
>15%	19.6%
>30%	25.0%
>50%	26.3%

14. Which <u>one</u> of the following issues relating to hemophilia gene therapy most concerns you?

Transient liver enzyme elevations	0.0%
The potential for clotting factor inhibitor development	0.0%
Long-term genotoxicity	48.4%
The high rates of pre-existing anti-vector immunity	14.1%
The inability for vector production capacity	3.1%
The inability to develop realistic costing strategies	34.4%

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

Inhibitors	35.4%
Supply/access to treatment products	60.0%
Pathogen transmission	1.5%
Other	3.1%

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

Inhibitors	81.7%
vCJD	0.0%
Viral transmission	8.3%
Unknown pathogens	10.0%

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

Price	85.1%
Regulatory issues	4.5%
Lack of manufacturing capacity	6.0%
Other	4.5%

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

Within the year	0.0%
Three years	25.8%
Five years	50.0%
Ten years	21.2%
Never	3.0%

19. Did this Global Forum…

Exceed your expectations	46.3%
Meet your expectations	47.8%
Not meet your expectations	6.0%

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