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THE 9TH WFH GLOBAL FORUM on Research and Treatment Products for Bleeding Disorders

October 22–23, 2015
Montreal, Canada
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WFH

WORLD FEDERATION OF HEMOPHILIA

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**9TH GLOBAL FORUM ON RESEARCH AND
TREATMENT PRODUCTS FOR BLEEDING DISORDERS**

Montreal, Canada

October 22-23, 2015

PROCEEDINGS

The World Federation of Hemophilia gratefully acknowledges
the sponsors of the 2015 WFH Global Forum:

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Thursday, October 22, 2015

Welcome and Opening

ALAIN WEILL, PRESIDENT, AND ALAIN BAUMANN, CEO/EXECUTIVE DIRECTOR, WORLD FEDERATION OF HEMOPHILIA

World Federation of Hemophilia (WFH) President Alain Weill welcomed 179 participants from 37 countries to the 9th WFH Global Forum on Research and Treatment Products for Bleeding Disorders, held in Montreal on October 22-23, 2015. This Global Forum combined for the first time with the WFH Research Forum, focusing on the latest research in hemophilia and current issues in safety, supply, and access to treatment products. Participants represented the broad range of stakeholders in the global bleeding disorders community; people with hemophilia and other inherited bleeding disorders, patient organization representatives, hematologists, clinicians, allied health professionals, academic and clinical researchers, blood services officials, and industry experts.

The program this year addressed key areas in hemophilia, including, surveillance of inhibitor development, barriers to access in the developing world, the changing economics of blood collection, tenders and procurement processes, gene therapy, novel treatment developments, and new therapies in the pharmaceutical pipeline. There were also presentations on the expansion of the WFH Humanitarian Aid Program, the WFH Research Program and its Clinical Research and Epidemiological Research Programs, and ongoing research by WFH clinical research grant recipients. “The bleeding disorders landscape and environment is in constant evolution, just as economics, science, and society continually evolve,” said Weill. “We must always be ready and aware of what is coming next in order to address these challenges successfully.”

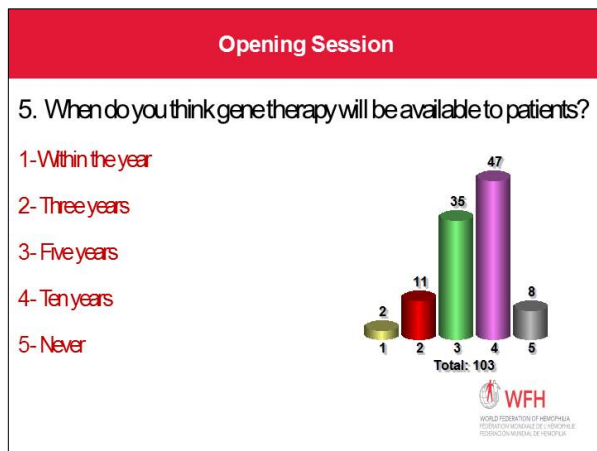
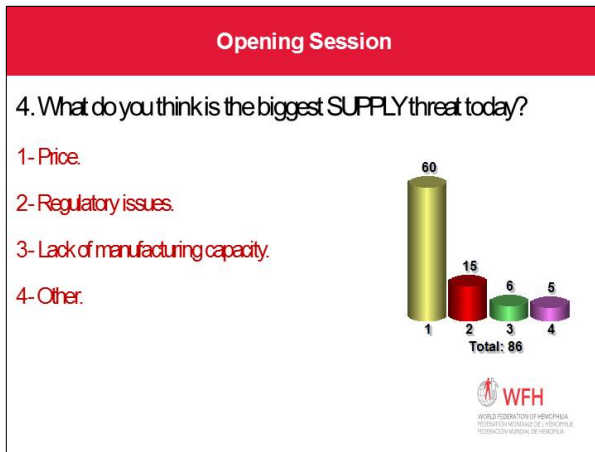
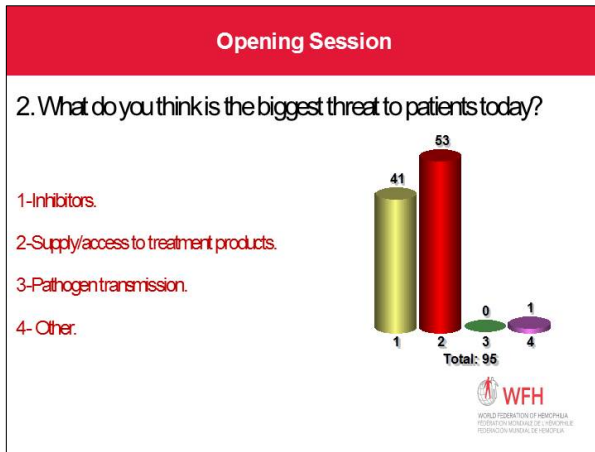
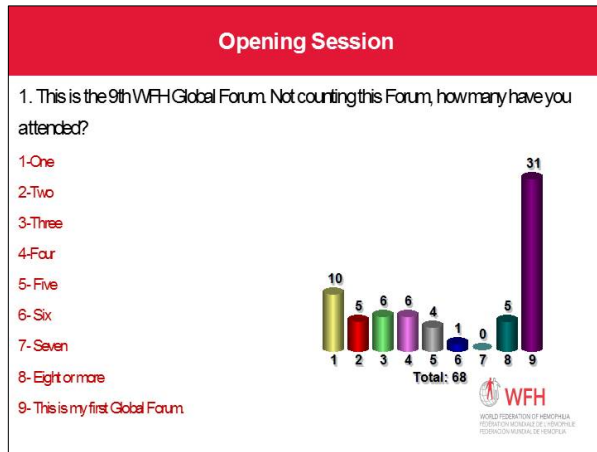
Weill went onto thank Brian O’Mahony, Chair of the WFH Treatment Product Safety, Supply and Access Committee (TPSSA), and Dr. David Lillicrap, Chair of WFH Research Committee, for their highly valuable contributions in planning the Global Forum.

WFH CEO Alain Baumann noted that the WFH has provided global leadership to improve and sustain care for people with inherited bleeding disorders for over 50 years. The vision is to achieve Treatment for All, regardless of where people with bleeding disorders live around the world. The WFH 2014 Annual Global Survey identified 287,066 patients with hemophilia and other inherited bleeding disorders in 106 countries worldwide. “With novel treatments poised to enter the market and gene therapy well along in the pipeline, we are entering a new era that we believe may bring WFH closer to our dream of Treatment for All,” said Baumann. “There are many unknowns in terms access, safety, and pricing, but one thing that is sure is that there will be a greater supply and variety of products.”

Moving forward, the WFH will continue to actively monitor access, safety, and supply developments as well as scientific and technological advances; advocate for access to adequate supply and safe and effective factor replacement therapies; and explore and develop collaborations to develop predictable and sustainable supply of treatment for the developing world through donations to the WFH Humanitarian Aid Program.

Baumann thanked the sponsors of the 9th WFH Global Forum on Research and Treatment Products for Bleeding Disorders for their funding and support: Baxalta, Bayer, Biogen, CSL Behring, Novo Nordisk, Octapharma, Sobi, Canadian Blood Services, Héma-Québec, and the Ministère de Relations internationales et Francophonie du Québec (Quebec Ministry of International Relations and Francophonie).

Throughout the meeting, the audience was polled on a series of questions to gauge their views on supply, safety and access issues in bleeding disorders treatment today.



SAFETY, SUPPLY AND ACCESS TO TREATMENT PRODUCTS

CHAIR: WILLIAM MURPHY, MEDICAL AND SCIENTIFIC DIRECTOR, IRISH BLOOD TRANSFUSION SERVICE

Blood safety and availability – current and emerging issues

ALBERT FARRUGIA, PHD, UNIVERSITY OF WESTERN AUSTRALIA

Prof. Albert Farrugia gave an update on current and emerging issues in blood safety and availability, and blood safety concerns surrounding transmission of hepatitis E (HEV), variant Creutzfeldt-Jakob disease (vCJD), parvovirus B19, multiple system atrophy prion disease, and hepegivirus.

Hepatitis E is the latest source of concern, with increasingly high levels of infectivity in normal blood donors. There are indications that viral inactivation procedures during fractionation are able to clear HEV, however, it is a small non-enveloped virus, which lends itself to some level of removal by nanofiltration.

Few new cases of variant Creutzfeldt-Jakob disease have been detected in the UK in recent years and the number of cases worldwide remains small. A single case of vCJD infection has been documented in a patient with hemophilia who had received factor VIII (FVIII) concentrate manufactured from UK plasma subsequently shown to have included a donor with vCJD. Clearance of prions in manufacturing is very high.

There are a number of measures in place that have decreased the risk of transmission of parvovirus B19. However, there continues to be detection of nucleic acids for B19 in batches of factor concentrates despite new measures such as DNA testing of pools of plasma and various inactivation steps.

Multiple system atrophy has been recently reported in the literature to be a new transmissible spongiform encephalopathy (TSE). This potential issue is not likely a problem as current inactivation processes clear prions very effectively but continued vigilance and efforts to eliminate risk are needed.

A new transmissible human hepegivirus (HHpgV-1) has been identified in blood transfusion recipients and hemophilia patients receiving plasma-derived factor concentrates. This virus is unlikely to be a source of concern as it is an enveloped virus, against which viral inactivation processes are fully effective. There are also many transmissible emerging and re-emerging pathogens that enter the blood supply such as the West Nile, Dengue, Ross River, and Hendra viruses.

Despite the growth in global demand for FVIII and increase in factor supply, about 75 per cent of people with hemophilia worldwide are still deprived of therapy. While the greatest increase in FVIII supply has come from recombinant sources, the demand for plasma-derived factor VIII has continued to increase. The increase in the developed markets has come from a continued adoption of prophylaxis and vigorous application of immune tolerance therapy for the eradication of inhibitors. Novel factor concentrates with extended half-life coming onto the market represent efficacious and safer recombinant factor concentrates, and are expected to have an impact on factor price and availability.

Discussion

Prof. Ted Tuddenham commented that discussions surrounding safety of bleeding disorder products still tend to focus on plasma-derived products, yet there are many newer treatment opportunities with

recombinant factor concentrates and variations of recombinant combinations. Prof. Farrugia concurred while noting that there are some areas of clinical use such as tolerization where there is still debate. Furthermore, manufacturing factor concentrates from plasma can be relatively cheaper than recombinant factor concentrates, and there remains a need for affordable plasma-derived therapies throughout the world.

Julie Birkofer of the Plasma Protein Therapeutics Association (PPTA) noted the shift in focus from concentrating on product features to concentrating on patient features as part of the trend to personalized medicine. Regarding availability, where are the challenges and what is necessary to provide personalized access to patients? Prof. Farrugia said there is a tendency in many parts of the world, particularly richer countries, to close down hemophilia treatment centres (HTCs) on the premise that they are not needed now that patients have home infusion. “Personalized prophylaxis is a good development in care but it needs to be guided properly—we will need very strong infrastructure over the next years to achieve it and assure that clinical outcomes are geared towards the individual patients,” he said.

A participant noted the issue of the cost of viral inactivation processes and asked whether there are new viral inactivation technologies not currently being applied for economic reasons. Prof. Farrugia said industry currently exceeds regulatory requirements regarding viral inactivation and enforces voluntary industry standards, thus are doing all that can be done without impediments related to cost. Eliminating non-enveloped viruses remains a challenge.

Impact of MSM donor deferrals on safety and supply

WILLIAM MURPHY, MEDICAL AND SCIENTIFIC DIRECTOR, IRISH BLOOD TRANSFUSION SERVICE

Dr. William Murphy described the current state of affairs regarding blood donor deferral policies on men who have sex with men (MSM). There are differences in practices and interpretations in blood collection worldwide. Some countries currently have a 12-month deferral (Australia, Brazil, Hungary, Japan, Great Britain), while others have a 5-year deferral (Canada, New Zealand). A number currently have a lifetime deferral (Northern Ireland, France, Belgium, the Netherlands, Germany, Switzerland, Austria, United States, China). The U.S. is moving towards a 12-month deferral and Canada is expected to as well.

A number of countries have moved away from a lifetime ban to a limited timeframe. From a safety standpoint, there are no data on the effectiveness of donor selection strategies at clinics and blood drives. However, for HIV and current emerging infection risks, at-clinic donor selection strategies may not be effective at all, especially for a pooled product.

The emergence of new infections and new technologies has had a major impact on the global ecology of blood and plasma therapies. There is now greater engagement with emerging and present threats: surveillance, curtailment, damage limitation, and early adoption of technological advances to deal with threat rather than disaster. Sterilization is a very effective way to prevent transmission of infectivity. There are very effective individual nucleic acid tests (ID NAT) for known viruses. With ID NAT testing, the effective risk period from donors with HIV infectivity is around two days.

Donor demographics are the major contributor to risk in the absence of effective ID NAT and sterilization. It is also how to measure whether a change in deferral has affected residual risk, if the sample is large enough. Analysis is incomplete to date, but it is clear that there is no change in the demographic risk for HIV in changing from a lifetime (or 10-year) ban to a lesser ban. Although further data

recategorization and statistical work is required, the countries that have changed can be very confident they have not added to patient risk for HIV. With emerging infections, the debate needs to be limited to new agents causing new diseases with very long incubation periods (e.g., HIV, HBV, HCV, vCJD; not malaria or Middle East respiratory syndrome coronavirus). It is important to assess and understand the incubation period of the disease between significant spread and recognition, between recognition and identification, between identification and testing, between testing and implementation of effective blood safety measures, and between recognition and effective blood safety measures.

Discussion

David Page of the Canadian Hemophilia Society said it has been known for some time that reducing the MSM donor deferral does not present a greater HIV risk and that a one-year deferral period is likely appropriate. However, there is also concern about the risk of emerging infections within that patient group. Why would a MSM donor who is negative for HIV, HCV and syphilis be considered a greater risk for unknown emerging infections than other donors? Dr. Murphy said it is important to analyse how to measure specific risks, and perhaps begin to segregate on the basis of exponential risk, e.g., enact a certain deferral period based on the donor's last multiple risk exposures, not just last MSM exposure.

Dr Alfonso Iorio said he was struck by the range of HIV rates in countries that reduced their MSM deferral periods and the finding that there is no change in the demographic risk for HIV in changing to a lesser deferral period. Is there information on whether any other changes adopted at the same time may have affected the rates? Is there evidence of what happened in countries that did not change their MSM deferral policies? Is there information on confounding factors affecting the HIV rates? Dr. Murphy said these issues must be investigated further.

Inhibitor development: Update on surveillance data and analysis

Report on EMA workshop on hemophilia registries

ANNELIESE HILGER, PAUL EHRLICH INSTITUTE, GERMANY; EUROPEAN MEDICINES AGENCY (EMA) BLOOD PRODUCTS WORKING PARTY

The key challenge with hemophilia registries is that there is no overarching structure for how to manage, design or host data collection, said Dr. Anneliese Hilger. Local, regional and international registries are organized by diverse groups such as HTC's, academic and clinical researchers, patient organizations, and pharmaceutical companies. Registries often focus on different aspects of the disease and collect different types of data. Dr. Hilger presented a summary of the European Medicines Agency (EMA) workshop on hemophilia registries held in London, UK, in July 2015. The workshop addressed who should have access to registry data, and whether the current number of registries improve patient safety and lead to better research in hemophilia.

The workshop reached a number of consensus points on what is needed to improve hemophilia data collection. Ideally, every patient should be in a disease registry. Patients enrolled in clinical trials should remain in registries. Patient identifiers are needed to avoid overlap between registries and reduce double-counting. The previously untreated patients (PUP) approach in EMA guidance needs review and further discussion. There is a need for collaboration among all stakeholders, including health technology assessment officials and patients. There is also a need for agreement with regulators and other stakeholders on a minimum protocol or dataset (parameters, minimization of bias, covariates/variables, confounding factors). It is also important to link with the initiatives of other rare disease registries as there

will be common issues. Finally, there is a need to harmonize national registries and promote and support more national registries and quality assurance.

Surveillance for inhibitors in the US

MIKE SOUCIE, PHD, CENTERS FOR DISEASE CONTROL (CDC), UNITED STATES

Inhibitors are the foremost complication faced by people with hemophilia today, associated with increased morbidity and mortality and a greatly increased financial burden, said Dr. Mike Soucie. All patients with hemophilia, whether severe or moderate, are at increased risk of morbidity and mortality from inhibitors; the level of risk for individual patients may differ based on various characteristics but everyone is at risk. However, with good prospective surveillance, inhibitors are potentially preventable.

The U.S. Hemophilia Inhibitor Research Study (HIRS) was initiated in 2006 as a pilot project for prospective national inhibitor surveillance with the aim to determine the feasibility of methods (testing and exposure data), identify the population at risk, and characterize inhibitor risk factors (genetic, treatment-related, and interactions). After following over 1,000 patients over six years, key findings of the HIRS study showed that centralized testing for inhibitors is feasible and reliable. The study resulted in the validation of testing methodologies and creation of a mutation database resource, and documented characteristics of patients with new inhibitors. This data confirmed that all hemophilia patients are at risk. Inhibitors occurred in patients with mild hemophilia, patients with low-risk mutations, and patients with over 150 exposure days—patients who had been considered at low risk.

National inhibitor surveillance requires a standardized protocol specifying the patients to be tested and testing intervals, as well as standardized, centralized testing. Confirmatory testing to eliminate false positives and incident inhibitor case surveillance for new cases are also important. This methodology could provide data on national incidence and prevalence of inhibitors. Ultimately, bleeding disorders registries, data collection and long-term surveillance provides powerful data on health outcomes, treatment complications and issues at different life stages. National surveillance allows monitoring of patients who develop inhibitors and how they respond to immune tolerance induction (ITI) therapy. Ongoing registry data collection is key to the development of prevention strategies and improvement in standards of care for bleeding disorder populations. Education and assessment of patient understanding about their risk of inhibitors and clinician understanding of inhibitor risk are essential, along with evaluation of the effectiveness of prevention strategies. Standards of care should include regular inhibitor screening as clinical indications cannot be relied upon to know the presence of inhibitors.

Report on FDA immunogenicity workshop

DR. GLENN PIERCE, MEDICAL MEMBER OF THE WFH EXECUTIVE COMMITTEE

Inhibitors present numerous challenges to different stakeholders, noted Dr. Glenn Pierce. He presented a summary report on the U.S. Food and Drug Administration (FDA) public workshop on new methods to predict the immunogenicity of therapeutic coagulation proteins held in September 2015.

For patients, caregivers and the healthcare system, the safety and efficacy of the drug is compromised, presenting economic costs as well as human costs in terms of increased morbidity and possibility of life-threatening circumstances leading to mortality. For industry, inhibitors present added risks to drug development costs and the lack of predictive tools means anti-drug antibodies are detected only in late phase 3 trials after significant expenses have accrued. For regulatory agencies, novel bioengineered products are becoming the norm, however, the immune consequences of neo-epitopes are difficult to evaluate. Furthermore, in small clinical trials, patients may not represent the full genetic diversity of proteins involved in immune response.

The FDA workshop focused on the genetic determinants of immunogenicity and highlighted the importance of well-characterized clinical samples. It also looked at resources such as hemophilia registries and databases, genotyping initiatives and biological samples. There was also important discussion on the use of previously untreated patients and how to better use this group to study immunogenicity, and the shift from hypothesis driven studies of individual genes to wider genomic studies and open hypothesis studies as researchers try to uncover the genetic components that contribute to immune response. The workshop also highlighted the importance of integrating data for better patient outcomes.

Novel engineered coagulation proteins emerging from the drug development pipeline present new concerns and greater risks have been identified for subsets of patients. With new advances in immunology, bioinformatics and computational biology, there is growing interest on the part of industry to use predictive tools for immunogenicity, Dr. Pierce said.

The ability to inexpensively generate and analyse vast amounts of genetic data is poised to foster a wave of disruptive technologies. Protein engineering, vector-based gene therapy, and induced pluripotent stem cells (iPSC) and transgene combinations offer unique scientific approaches toward disease management and cure. Large datasets are increasingly being used in all therapeutic areas—an important question is how to better use these tools in the bleeding disorders community. “How industry and regulatory agencies respond to the new technologies will determine how much patients benefit,” Dr. Pierce said.

Immunogenicity remains an unresolved issue. “Virtually all biotechnology drugs provoke immune response in some patients, though usually just tiny fractions. However, the reactions are becoming of greater concern as the number of protein drugs increases,” he said.

EMA guidelines on transparency for clinical trials

MARIJKE VAN DEN BERG, UNIVERSITY HOSPITAL UTRECHT, THE NETHERLANDS; WFH VP MEDICAL

Dr. Marijke van den Berg gave an overview of the new transparency guidelines put forth by the European Medicines Agency within the EU Clinical Trials Regulation, which come into action on May 28, 2016. The underlying principle of the new transparency guidelines is that patients, physicians and other healthcare workers will have insight into all information concerning clinical trials; this includes details of the clinical trial protocol, date of start of inclusion and number of subjects in the trial, and any changes of the protocol during the clinical trial. The objective is to make available a summary of all clinical trial results accessible while respecting the privacy of patients and persons working in the trials, to create a knowledge management resource in order to foster innovation and stimulate and accelerate further research. This aims to avoid unnecessary duplication of clinical trials, repetition of trials that have been terminated due to major safety or efficacy failures, and repetition of trials that have demonstrated such failures even if the trial was completed.

The new guidelines delineate what must be made public before, during, and at the end of every clinical trial. Companies are required to publish the results of a clinical trial within a year of its ending, and required to prepare a report within 30 days after marketing authorization has been granted or marketing authorization has been withdrawn. Data that are not accessible include personal data, commercially confidential information, confidential communication between the member states in the preparation of their assessment, supervision of clinical trials by the member states, and the position of the EU Data Safety Monitoring Board. “Patients’ privacy must be protected by adequate policy and technological measures especially in rare diseases, where patient-level data could potentially be identifiable,” Dr. van den Berg emphasized. Commercially confidential information should also be protected to avoid discouraging companies from providing access to clinical data, she added.

Discussion

Dr. Alok Srivastava asked whether it would be possible to download data on patients from different studies to perform different analyses. Dr. van den Berg said this is not currently possible, but will be in the future. She added that it is important to recognize that in hemophilia, with the limited number of subjects in clinical trials, the information is too limited to make conclusions on the safety of the products.

Dr. Anneliese Hilger noted that the EMA transparency guidelines have been initiated hand in hand with the new clinical trial application law and this implies that in future in Europe there will be a single place to apply for conducting multinational trials; the process and details are still under discussion. There may need to be a two-step system, with one stage to address application details and the ongoing clinical trial itself and another stage to address clinical outcomes and results once the trial has been terminated.

Patient organizations should be more demanding in terms of post-marketing surveillance and the creation of a patient education program to declare adverse events—specifically inhibitors, said Thomas Sannié of the French hemophilia association. Previously untreated patients seem to be the population to study and understand the basics of immunogenicity—how do investigators handle the ethical issue of exposing PUPs to such a risk? Dr. Pierce said the entire bleeding disorders community needs to take full responsibility for inhibitor development and the lack of progress. Clinical trials are currently designed sequentially for adults, adolescents, children, and then PUPs. He proposed a different utilization of PUPs to enable looking at ways to limit inhibitor formation in clinical trials for PUPs, as well as ways to treat them once inhibitors form. It is important to ensure that products are safe and effective before introducing them to children.

Barriers to access in the developing world

ALBERT FARRUGIA, PHD, UNIVERSITY OF WESTERN AUSTRALIA

The main barriers to access to hemophilia medicines and care in the developing world, and in developed countries alike, are economic constraints and largely a function of economic status and development as well as societal or governmental priorities, said Prof. Albert Farrugia. Data from the 2014 WFH Annual Global Survey on average global FVIII use per capita based on World Bank rankings show that people with hemophilia who live in countries with higher economic rankings tend to have good or reasonable access to treatment, while those in lower ranking countries generally have suboptimal or virtually no access to treatment. In addition to access and cost of hemophilia treatment, key challenges in the developing world are lack of diagnosis and insufficient blood collection.

There are a variety of possible solutions to address the inadequate access to care and safe treatment products in the developing world. The WFH's Project Recovery is a humanitarian aid initiative in collaboration with Biotest, which transforms unused cryoprecipitate from the developed world into safe factor concentrates for the developing world. The Italian Blood Services in collaboration with Kedrion is developing a similar initiative, which it aims to embed in the blood system. "By having these programs, bleeding disorder patients will get a voice, with the goal being that they will ultimately get sustainable treatment programs," Prof. Farrugia said. "Any kind of aid needs to be geared to the commitment of the people receiving the aid."

Ultimately, advancing treatment possibilities in the large, under-developed countries hinge on the development of blood systems and biopharmaceutical capacities. Some of the countries, such as China and India, are already significant players in global biopharmaceutical manufacturing. Continual technological advances leading to increased production capacity and enhanced safety and supply also offer optimism for access to better treatment in the developing world.

Changing economics of blood collection

KATHLEEN ROWE, DIRECTOR OF PLASMA AND MARKET DEVELOPMENT, BLOOD CENTERS OF AMERICA (BCA)

Kathleen Rowe described the changing economics of blood collection in the United States and the pressures that blood centres are under to fulfill their missions to provide lifesaving blood products. U.S. blood centres are currently under considerable price pressures. For example, the Centers for Medicare and Medicaid Services recently proposed cutting reimbursements to hospitals for blood products by 40 per cent. Additional pressures include aging donor populations (e.g., apheresis donors) and the need to recruit younger donors, as well blood utilization pressures. In terms of demand, data from U.S. blood centres on red blood cell distributions from 2010 to 2014 show a clear decline. Tracking of red blood cell demand by Blood Centers of America (BCA) showed a 4 per cent decline from 2011 to 2012 and the declining trend has continued in 2013, 2014 and 2015, by about 6% each year.

All blood centres are striving to increase efficiencies; some are looking to specialize or diversify products or collect and distribute products differently; and some are merging to consolidate costs and support functions. Traditionally, centres would put out a call for as many blood donors as possible and following blood collection would separate the whole blood into its components, red blood cells, and plasma. Red blood cell demand was the market driver for blood collection, similar to how intravenous

immunoglobulins (IVIG) are the market driver for plasma. Plasma was made if fresh frozen plasma (FFP) was needed for transfusion, and if not it became recovered plasma sold for fractionation. As red blood cell use declines, it is imperative that centres understand the real needs in the hospitals and match how they handle blood donors with the real-time needs of hospitals. In the new demand-based blood collection model, centres must monitor hospital blood needs by gender, product and blood type in order to decide how to handle individual donors to get the most out of donations and produce the right product needed at the right time.

Meanwhile, demand for plasma-derived products is increasing. Data from the Marketing Research Bureau show substantial increases in worldwide demand for both plasma-derived and recombinant FVIII from 1984 to 2014; while demand for recombinant factor has dominated in recent years, demand for plasma-derived products continues to grow. Many blood centres are now focusing on the collection of source plasma to meet the plasma demand, which aligns with the mission to save lives and support plasma product availability and leverages the expertise and capacities within centres that already manage apheresis donors and have systems in place to handle the complexities of collection and distribution.

Tender and procurement – challenges and opportunities

BRIAN O'MAHONY, CHAIR, WFH TREATMENT PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE (TPSSA)

Brian O'Mahony shared insights on the new EU procurement directive, challenges related to health technology assessments (HTAs) and extended half-life therapies, and opportunities to provide access to factor products to developing and emerging countries. Currently, 19 European countries as well as Brazil, Canada, Australia, South Africa, Mauritius, Iraq, Central America, and Saudi Arabia and the Gulf States carry out tenders to purchase factor concentrates. Another 19 European countries do not use a tender process, including many original Eastern European member states of the EU, as well as the United States, China, and Thailand, which all have alternative procurement processes.

The increased involvement by HTA bodies and economic evaluation of new products before going to tenders in many countries will be a significant challenge for new extended half-life factor concentrates. If the cost of treatment is greater than the current cost, the HTA will look at the incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY). Extended half-life factor concentrates will possibly have difficulties with HTA processes in several countries if the cost is significantly higher, therefore there needs to be clear clinical data to demonstrate the significant benefits. As extended half-life products come to market, the price of current recombinant products decreasing. This presents the opportunity for some countries to increase per capita use of recombinant factor concentrates. It is important to ensure that clinicians and patient organizations are formally involved in tender and procurement processes, as they understand the value and cost of the products. Optimum assessment of products examines efficacy, safety, quality, supply, and scientific support. Clinician and patient involvement lead to better products and outcomes, and cost-effective treatment.

The new EU Procurement Directive (2014/24/EU) allows increased discussion under the competitive dialogue procedure with negotiation, and consideration of life cycle costs and the inclusion of auxiliary benefits such as HTC support staff, electronic devices and home delivery in tenders for factor concentrates. In 2015, the province of Quebec, Canada, carried out the first tender to include both current generation factor concentrates and extended half-life factor products, using scoring criteria for quality and other characteristics, then factoring in price, and applying a correction factor to extended half-life products based on an estimate of lower number of units required.

Discussion

The novel therapies and extended half-life factor products are not comparable to the current generation factor concentrates—how do tender and procurement processes deal with this issue? a participant asked. European countries have not yet had to address this issue as extended half-life products are not yet licensed there, said Mr. O'Mahony. In the U.S., the products were launched at an increased price per unit almost in line with the reported extension in half-life. Canada made its own assessments based on the number of units of current recombinant products required compared to units of extended half-life products and applied their own correction factor, corresponding to an estimate of the expected decrease in units required. It would also be feasible to compare product prices in terms of how much of each treatment product would be needed to achieve a specific trough level.

Over the past 30 years, the emphasis in hemophilia worldwide was on improving care—however, currently in the western world, the emphasis is on reducing costs such as through tender processes or health technology assessments, Dr. Manuel Carcao said. Yet there are studies that show that current treatment in the western world is not optimal particularly on a longterm basis, let alone in the 75 per cent of the world with no treatment. Hemophilia treatment can still improve a great deal and yet the current emphasis is on costs.

Expansion of the WFH Humanitarian Aid Program

DR. ASSAD HAFFAR, WFH HUMANITARIAN AID DIRECTOR, WORLD FEDERATION OF HEMOPHILIA

Dr. Assad Haffar outlined the expansion of the WFH Humanitarian Aid Program to improve access to safe and effective treatment products in the developing world. The WFH Humanitarian Aid Program was started in 1996 with 2,879,130 IUs of surplus factor concentrates donated by pharmaceutical companies. In the years since, the WFH has distributed over 266 million IUs to 87 countries, helping over 90,000 persons with hemophilia and other bleeding disorders. Donated products are sent to registered HTC's and WFH national member organizations (the registered hemophilia society in each country). Dr. Haffar described some of the experiences WFH staff and volunteers have had with people with hemophilia in developing countries in need of treatment products. Within the past month, the Humanitarian Aid Program rushed donated factor concentrate to Nigeria to provide life-saving treatment for a young boy. The WFH also provided factor to resolve a wrist hematoma on an adolescent boy in Togo, allowing him to return to school and a normal life, and reach the top of his class. In Egypt, the WFH provided treatment product which allowed a young boy to have corrective surgery for a wrist hematoma. In Senegal, WFH humanitarian aid product resolved a young patient's knee compartment syndrome.

To address the need, there must be predictable and sustainable access to treatment products for all persons with hemophilia and other bleeding disorders. This requires increasing the amount of donated products that the WFH collects from its sources, improving training for health professionals in all developing countries, and seeking multi-year donations to ensure a steady flow of treatment products to the WFH network and make it possible for people with bleeding disorders in the developing world to have access to treatment for emergency situations, acute bleeds, corrective surgeries, and for young children with hemophilia to have prophylaxis.

The goal of global access to predictable and sustainable access to treatment products cannot be achieved by the WFH alone—it requires an expansion of the WFH's collective effort with companies, countries,

and the global hemophilia community. The ongoing expansion of the Humanitarian Aid Program aims to increase WFH donations of FVIII and FIX to meet the increased demand in developing countries; ensure that product donations are more predictable (particularly in terms of shelf-life, quantities and timeline); and help establish special agreements and treatment programs with recipient countries. With predictable and sustainable access to products, healthcare professionals in developing countries will be able to treat patients according to international hemophilia treatment standards and WFH treatment guidelines, including the possibility to perform corrective surgeries and establish prophylaxis programs. Beyond improved treatment, predictable and sustainable access to products allows better hemophilia outreach, diagnosis and training.

Discussion

Brian O'Mahony asked how WFH will go about training physicians on how to use extended half-life factor concentrates. Dr. Haffar said as these products only recently entered the market, thus far the WFH has prepared the first fact sheets on product dosage and how to use these products for acute bleeds, surgery and prophylaxis. Training on extended half-life products will be part of a complete training on hemophilia treatment.

Dr. Ted Tuddenham asked what will happen when large amounts of high-purity recombinant and extended half-life products are introduced in developing countries, particularly in Africa where there used to be no product available. Will there be an inhibitor outbreak in these places? Dr. Haffar said inhibitor development due to extended half-life products is a major issue being discussed by the WFH Medical Advisory Board. There has been no increase in inhibitors thus far, but inhibitor development is a risk that could happen. One solution is to have more access to bypassing products.

Ahmed Abdelbari of the public healthcare provider of Qatar noted that almost 70 per cent of people with hemophilia worldwide do not have access to treatment and asked whether WFH will set objectives for how many people will receive factor concentrates through the Humanitarian Aid Program. Dr. Haffar said the program responds to the most urgent need. Data collected in the WFH Annual Global Survey shows the number of people diagnosed in each country, and the need in each country can thereupon be calculated. However, the WFH is not able to respond to every need of every patient in every country.

Dr. Gary Gilbert said there may be a certain level of risk in educating physicians and other providers on the nature of hemophilia and the need for diagnosis in clinical conditions, but then not have sufficient products to effectively treat patients. Dr. Haffar said there is no harm to start diagnosis of patients and training for physicians, physiotherapists, nurses and others while trying to improve supply in a country and start procuring treatment products.

How to measure progress in the provision of care for hemophilia

ALFONSO IORIO, ASSOCIATE PROFESSOR, DEPARTMENT OF CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS, MCMaster UNIVERSITY, HAMILTON, ONTARIO, CANADA; CHAIR OF WFH DATA AND DEMOGRAPHICS COMMITTEE

Dr. Alfonso Iorio described an ongoing project of a workgroup of the WFH Data and Demographics Committee, looking into the development of simple measures that can be calculated based on available data to be used for benchmarking and measuring progress in hemophilia care over time. It is often cited that 80 per cent of people with hemophilia A have no access to FVIII therapy, based on a figure put forth by Dr. Peter Jones in 1995. Then in 2003, Dr. Jones and Line Robillard, then WFH executive director, stated that the 80 per cent estimate was not based on any specific worldwide demographic information on

hemophilia.

A WFH Data and Demographics Committee Workgroup (Alfonso Iorio, Jeffrey Stonebraker, Mark Brooker and Mike Soucie) has now taken up the task to calculate the progress in the provision of hemophilia treatment since the 1990s. The aim is to try to identify simple indicators of healthcare coverage and quality of care for people with hemophilia; it does not concern treatment products alone (IUs per capita or effective units) but rather attempts to assess the quality of hemophilia care as a whole. Its specific focus is on demographic measures for cross-sectional and longitudinal evaluation, and cross-sectional benchmarking between different countries. Its methods involve longitudinal analysis of data from the WFH Annual Global Survey and other demographic sources, exploratory calculations by repeating assessments over different countries, and proposed interpretation.

Thus far, the workgroup has identified three indicators—rate of missing (or unidentified) patients with hemophilia, proportion of severe patients with hemophilia, and survival of patients with hemophilia—as a way of measuring hemophilia care performance, using WFH global survey data. This would be useful for advocacy by providing data on the state of care and areas requiring improvement, and as an index to convey to WFH stakeholders the impact of hemophilia care and changes over time in specific countries.

Discussion

The workgroup's approach to measuring progress in the provision of care for hemophilia is interesting and feasible, however, they must be very careful to ensure that the observed numbers taken from the global survey are correct, said WFH VP Medical Marijke van den Berg. In the developing world, and even in the United States, not all patients are in these denominators. Dr. Iorio agreed and said the indicators also serve as an internal check of the global survey data. The investigators will assess whether or not data collection methods and the quality of data available are reliable for developing measures, or whether there is a need to try improve the quality of data being collected.

In most developing countries, there are variations in the rate of people with hemophilia identified and percentage of severe hemophilia patients that are not easy to understand—it's an immense challenge to come up with a general figure that could apply broadly to different countries, Dr. Alok Srivastava said. Dr. Iorio agreed and said the WFH Data and Demographics Committee has introduced checks in the global survey to determine whether the figures being reported by countries are guesses based on expected prevalence for the population size, or figures based on actual data and incidence.

Data must be interpreted on the basis of individual countries, as data from each country will be specific to the way the data is collected locally, Dr. Soucie said. For example, the U.S. data reported to the WFH global survey is based only on patients who receive care in federally funded HTC's.

Inclusion of DDAVP on WHO Essential Medicines List and implications for access

MARK BROOKER, SENIOR PUBLIC POLICY OFFICER, WORLD FEDERATION OF HEMOPHILIA

Mark Brooker described the WFH's successful efforts to have the World Health Organization reinstate demopressin acetate (DDAVP) on the WHO Essential Medicines List. DDAVP is a synthetic hormone manufactured in many countries worldwide. It is efficacious in the treatment of patients with mild hemophilia A and patients with von Willebrand disease (VWD), and also reported to successfully prevent or treat bleeding in patients with mild platelet function defects and vascular abnormalities. It is a very

affordable treatment for hemophilia and VWD in developing countries with limited access to factor concentrates.

Desmopressin was added to the WHO Essential Medicines List in 1992, and then deleted in 2003 as it was deemed by reviewers to not be an essential medicine. Over 2014 and 2015, the WFH applied to have DDAVP returned to the list on the basis that it is safe, efficacious, affordable and evidence-based treatment for rare diseases. The WFH application was supported by multiple stakeholders including factor concentrate manufacturers, international bleeding disorder societies, national blood services, individual hematologists, trade and industry associations, and charitable organizations. DDAVP was reinstated on the list in June 2015 after a public consultation and review by the WHO Expert Committee. In the WFH 2014 Annual Global Survey, more than half of 127 WFH National Member Organizations (NMOs) report that DDAVP is available for hemophilia A and VWD and being used in their countries. There is a large group of countries where it is not being used due to different issues such as DDAVP not being licensed in the country possibly in part because it is not a highly profitable drug. The WFH will strive to leverage DDAVP's return to the WHO Essential Medicines to get access for more patients around the world.

Discussion

A participant noted that some countries have access to DDAVP but do not use DDAVP for VWD and asked whether it is possible in such cases to make the diagnosis of VWD. Mr. Brooker replied that it is possible that VWD is not being diagnosed in some of these countries, which may be why DDAVP is not being used there. Dr. Alfonso Iorio said DDAVP is used in Canada but in some cases patients may have access to factor concentrates covered through the healthcare system, whereas DDAVP is not covered and patients would have to rely on private health plans or pay out of pocket. Adding DDAVP to Canada's essential medicines list would give patients access or provisions for DDAVP. Dr. Alison Dougall of the Dublin University Dental Hospital noted that DDAVP can be used effectively as prophylaxis prior to dental surgery in patients with mild/moderate hemophilia and VWD, however, there is a large gap in the actual use of DDAVP in dentistry.

Outcomes of low-dose prophylaxis in children

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

It is well established that prophylaxis started early in life reduces or prevents musculoskeletal problems and it is therefore recommended that prophylaxis should be the treatment of choice for people with severe hemophilia and started at least after the first joint bleed. The main objective of primary prophylaxis is to reduce the number of joint bleeds by maintaining the patient's plasma FVIII or FIX levels above 1 IU/dL. Prophylaxis has demonstrated efficacy in reducing the annual number of major bleeds, clinic visits and hospitalization, and the development of arthropathy. Regular prophylaxis is associated with a 60 per cent lower risk of inhibitor development than on-demand treatment. Dr. Magdy El Ekiaby described research into prophylaxis using lower doses of factor concentrates and its efficacy and feasibility in resource-limited settings and the experiences in three countries in Africa and the Middle East: Tunisia, Algeria and Egypt.

In Tunisia, the prophylaxis protocol was adapted for hemophilia A (20-30 IU/kg once a week, 20 IU/kg twice a week, 10-15 IU/kg three times a week, with clinical evaluation after one month) and hemophilia B

(25-35 IU/kg once a week, 15-25 IU/kg twice a week, with clinical evaluation after one month). The weekly median consumption was 30 IU/kg/week in both hemophilia A and hemophilia B. The study was initiated in 45 children and collected data on the mean age of initiation, number of annual bleeds, hemophilia joint score, functional independence score in hemophilia, school absenteeism, quality of life, and hemophilia quality of life (Hemo-QoL). There was a significant reduction in the total annual bleeding, from 460 total bleeds before prophylaxis to 42 bleeds after prophylaxis. School absenteeism also decreased, from once or twice a week to one or zero days per year, and there has been significant improvement in quality of life, with the children able to live almost normal lives.

In Algeria, longterm follow-up, with regular clinical evaluations over two years, allowed researchers to assess the effectiveness of a low-dose prophylaxis protocol in the prevention of arthropathy. The observational, prospective and descriptive study found primary low dose prophylaxis to significantly reduce bleeding episodes including hemarthroses (particularly in the knees) and maintain joint function and avoid motor disability in children with severe hemophilia, and with consumption of FVIII amounts similar to on demand treatment. In Egypt, primary data on low-dose prophylaxis indicate that it reduces annual bleed rates, and preserves musculoskeletal health and hence physical, mental and social activities. The primary data can be used to model longterm needs.

Discussion

Low-dose prophylaxis is certainly better than on-demand therapy but it is important to keep in mind that it is only the starting point for achieving prophylaxis, said Dr. Emma Goulder of Tunisia. A low dose is appropriate for introducing prophylaxis in children but adults would need a greater amount of factor concentrate. Therefore low-dose prophylaxis aims to improve the level of care step by step, but it is not the final point. In Tunisia, there are now patients on low-dose prophylaxis with over five years of follow-up. The low-dose regimen has shown to improve quality of life and reduce annual bleeding rates; patient education on compliance has been key. On the other hand, children are not allowed to participate in certain physical and sports activities. Therefore, it is only a starting point to improving care. Dr. Alok Srivastava added some countries may not think they have sufficient factor to introduce prophylaxis, when a low-dose approach would possibly be feasible with their current factor supply. He noted that early hemophilia prophylaxis used significantly lower doses than used today, yet achieved reductions in bleeding. In this way, countries should gradually increase their per capita factor use; the actual amount of factor considered ideal for prophylaxis is another matter for debate. In the end, there must be the same goal everywhere—no joint damage—whether that's achieved by 1, 2 or 3 bleeds per year.

Brian O'Mahony asked whether the expansion of the WFH Humanitarian Aid Program would be able to provide sufficient aid to enable some countries to initiate low-dose prophylaxis and how progress would be measured. Dr. Assad Haffar said one of the objectives is to start low-dose prophylaxis in children under two years of age. There are many considerations, including the development of measures to track treatment progress in reducing bleed rates and joint damage in children. The WFH Humanitarian Program would also welcome donations of other bleeding disorder therapies such as DDAVP and tranexamic acid.

FRIDAY, OCTOBER 23, 2015

RESEARCH

Novel developments in treatment of bleeding disorders

CHAIR: DAVID LILLICRAP, CHAIR, WFH RESEARCH COMMITTEE

Factor VIII mimetics

MIDORI SHIMA, MD, PHD, DEPARTMENT OF PEDIATRICS, NARA MEDICAL UNIVERSITY; HEAD OF NARA HEMOPHILIA TREATMENT CENTRE, KASHIHARA, JAPAN

Dr. Midori Shima described the new bispecific antibody therapy ACE910, which holds promise as a new treatment for hemophilia A. Activated FVIII functions as a cofactor for FIXa catalyzed FX activation. The role of FVIIIa can be considered to support suitable interaction between FIXa and FX and enhance tenase reaction. ACE910 is an asymmetric bispecific antibody that recognizes FIXa and FX, and can support their interaction like native FVIIIa, thereby promoting FX activation and accelerating further coagulation reaction.

Dr. Shima described a first-in-patient phase 1 clinical study that investigated the safety, pharmacokinetic and pharmacodynamic profiles of ACE910 in severe hemophilia A patients as well as its prophylactic efficacy on bleeding. After 12 weeks' observation in the phase 1 study, investigators continued the clinical study for hemophilia A patients as an extension study in all three cohorts, using the same corresponding doses as in the phase 1 study. A total of 93 adverse events were reported in 18 patients. All were of mild or moderate intensity. Most of the related adverse events were injection site reactions; one unrelated severe adverse event was observed after treatment withdrawal. No thromboembolic adverse events were reported, even when FVIII or bypassing agents were given under ACE910 prophylaxis to treat breakthrough bleeds. Three patients developed anti-ACE910 antibodies, however, all of them were non-neutralizing antibodies and none affected pharmacokinetics or pharmacodynamics. The median annual bleeding rate was markedly reduced in all cohorts. Joint bleeding was well controlled, with median annual bleeding rates of zero. Four patients with inhibitors received on demand therapy with bypassing agents. Three inhibitor patients received prophylactic treatment with bypassing agents before administration of ACE910. All non-inhibitor patients received prophylaxis with FVIII, which maintained promising efficacy throughout follow-up. In almost all patients, ACE910 remarkably reduced bleeding rate irrespective of the presence of inhibitor.

FVIII relative activity estimated from in vivo study suggests that ACE910 can be applied to first-line prophylaxis maintaining mild factor levels for complete prevention of bleeding. Furthermore, it may be possible to apply to hemostatic treatment too. Though ACE910 is very promising so far, more clinical data is needed.

Non-factor replacement strategies: Anti-coagulant inhibition

GARY E. GILBERT, ACTING CHIEF, HEMATOLOGY SECTION, VA BOSTON HEALTHCARE SYSTEM, MASSACHUSETTS, USA

Dr. Gary Gilbert described novel non-factor replacement strategies, including an alternative and novel approach called anticoagulant inhibition treatment which inhibits the proteins that prevent clotting; and natural anticoagulants such as tissue factor pathway inhibitor (TFPI) and antithrombin III (ATIII) which restore balance by inhibiting the anticoagulant proteins.

Several new agents in clinical trial have offered hope for hemophilia treatment without requiring FVIII or FIX concentrates:

- ACE910 by Genentech-Roche is a FVIII mimetic bispecific antibody that targets FIXa. It could be given weekly by subcutaneous injection; however, there is a risk that it may not achieve completely effective rescue with FVIII if there is breakthrough bleeding.
- ALN-AT3 by Alnyam is an ATIII therapy based on inhibitory RNA that decreases the plasma levels of ATIII (rather than inhibiting ATIII). It could be given monthly by subcutaneous injection; however, there may be a thrombosis risk when one needs rescue with FVIII or FIX.
- BAX499 by Baxalta was in phase 1 clinical trial but is no longer under development. It targeted TFPI but showed a risk of excess bleeding tendency and possible increased thrombotic risk, highlighting the complexity of TFPI inhibition.
- Concizumab by Novo Nordisk is a monoclonal antibody. It could be given weekly or monthly by subcutaneous injection; however, there may be a thrombosis risk when one needs rescue with FVIII or FIX.

Preclinical and early clinical data suggests FVIII mimetic and anti-inhibitors may not be as effective as FVIII or FIX but they are likely to be good enough for the treatment of inhibitor patients and possibly for primary prophylaxis with weekly to monthly subcutaneous dosing. Concerns to watch for include whether these novel therapies can be used successfully during rescue with bleeding episodes with FVIII (ACE910) or FIX (ALN-AT3, Concizumab); whether prophylaxis dosing is adequate, particularly for the long term (the cumulative effect of minor bleeding episodes may be qualitatively different); and whether the therapies carry thrombotic risk, particularly during rescue with FVIII or FIX.

Prolonged-half life products: current clinical practices

MANUEL CARCAO, MD, MSC, CO-DIRECTOR, HEMOPHILIA CLINIC, HOSPITAL FOR SICK CHILDREN, TORONTO, CANADA

Dr. Manuel Carcao gave a brief overview of extended half-life FVIII and FIX therapies and described some clinical data and key study results and findings. There are a number of extended half-life FVIII products under development or already licensed for the market. The next generation recombinant FVIII Fc fusion protein (rFVIII Fc) Eloctate[®] manufactured by Sobi in partnership with Biogen was approved by the U.S. Food and Drug Administration (FDA) and Health Canada in 2014. There are also several different pegylated therapies in the pipeline including Bayer's novel longer-acting factor VIII compound, BAY 94-9027, based on single B-domain deleted site-specific pegylation; Novo Nordisk's glycopegylated B-domain truncated recombinant FVIII, N8-GP; and Baxalta's new extended half-life FVIII therapy based on controlled pegylation of full-length FVIII, BAX 855 (the drug, called Adynovate was approved by the FDA in November 2015). Despite the differences, these novel therapies all offer similar extended half-life and similar pharmacokinetics. Phase 1 pharmacokinetic studies found considerably extended half-life by

1.4 to 1.6 times. Eloctate[®] administered at the same frequency as the conventional FVIII product Advate[®] allows for higher trough levels, or fewer infusions to achieve the same trough level. Pivotal phase 3 studies on BAX 855 showed extended half-life by 1.4 times, providing an extra day of protection per infusion; 70.4 per cent of patients treated on prophylaxis were able to decrease frequency of dosing with at least one infusion less per week.

There are also different extended half-life FIX products in the pipeline; Biogen's Fc fusion FIX product (now licensed as Alprolix[®]); Novo Nordisk's glycopegylated B-domain truncated recombinant FIX, N9-GP; and CSL Behring's albumin fusion protein, FIX-FP. All three novel FIX therapies show significant extended half-life by three- to five-fold in comparison to standard FIX concentrates, allowing much higher trough levels per infusion, or significantly fewer infusions required to achieve the same trough levels of standard therapies (e.g., N9-GP would require one infusion every 7, 10, 14 days or more, substantially fewer infusions than the twice weekly infusions required with conventional FIX therapies). The studies suggest that once weekly dosing may be possible for hemophilia patients and many are likely to do well with dosing every two weeks. Alprolix[®] and N9-GP have demonstrated good safety so far. Clinical study results also show lower annual bleed rates with these novel therapies.

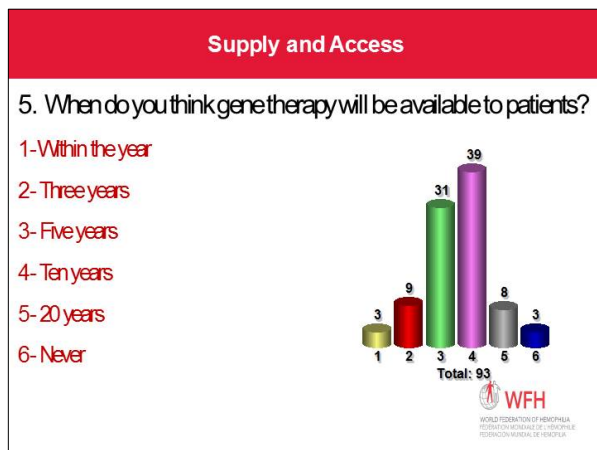
Studies of extended half-life FVIII and FIX products in adults and children with hemophilia are showing that patients can reduce frequency of infusions while maintaining very low bleeding rates. Patients are primarily choosing less frequent infusions and not much higher trough levels. Patients who try these extended half-life products are content and do not want to go back to the conventional factor products. Quality of life is better with extended half-life products, but better QoL measurements are needed. More individualization of prophylaxis is likely possible with these extended half-life factor concentrates. It is too early to make conclusions from studies on previously untreated patients regarding inhibitor development but the current hope is for lower incidence of inhibitors.

Discussion

Dr. Robert Montgomery of the U.S. Blood Research Institute noted that newborns are prone to bleeding and thrombosis because they have reduced vitamin K protein and ATIII enzyme levels, resulting in dysregulation that leads to potential for bleeding and clotting issues. He expressed concern that non-factor strategies that rebalance hemostasis by inhibiting anticoagulant proteins could compromise the checks and balances in the hemostasis system.

Dr. Keith Hoots of the U.S. National Heart, Blood and Lung Institute noted that thrombosis is a potential serious adverse event with some of the novel therapies when one needs rescue with FVIII or FIX, particularly microvascular bed thrombosis. What will happen when a patient suffers serious trauma, for example, in an automobile accident. Dr. Gilbert suggested it might be necessary for the patient's medical alert bracelet or card to specify that the patient requires both ATIII and FVIII or FIX administered at the same time.

Overall, people in the bleeding disorders community appear to feel reasonably comfortable with extended half-life products and substitution therapy, said Dr. Carcao. Even a therapy that generates above 20% FIX trough levels does not seem to be of great concern in terms of potential risk for thrombosis as it is still substantially lower than the 100% trough levels in people who do not have hemophilia. More study is needed of the trough levels achieved by different types of products and whether these trough levels reduce bleeding rates. However, some novel therapies act by altering the patient's coagulation cascade at the molecular level, so there is cause for concern about their effects.



Gene therapy update

EDWARD TUDDENHAM, MD, KATHARINE DORMANDY HAEMOPHILIA CENTRE, ROYAL FREE HOSPITAL, AND UNIVERSITY COLLEGE LONDON, LONDON, UK

Dr. Ted Tuddenham presented data from an ongoing phase 1/2 clinical trial of gene therapy of hemophilia B and described findings from longterm follow-up of six patients in the initial dose escalation cohort and four additional patients recruited to an expanded high-dose cohort. He also discussed plans for gene therapy of hemophilia A.

Adeno-associated viral vectors (AAVs) for hemophilia gene therapy offer the best safety profile amongst viral vectors. They offer reduced risk of immune response to viral proteins. A single administration of the vector into liver results in stable longterm transgenic factor expression from episomal proviral genomes. The UCL Haemophilia B Gene Therapy Trial is designed with phase 1 dose escalation. The objective is to assess the safety and efficacy of a bolus peripheral vein infusion of the novel self-complementary adeno-associated virus vector (scAAV2/8-LP1-hFIXco) on patients with severe hemophilia B with FIX levels below 1% of normal. In the initial phase of the study, six subjects received the novel scAAV2/8-LP1-hFIXco, with two subjects treated at each of three dose levels. Results showed evidence of sustained FIX expression at 1-5% levels in all six subjects for over three years. Three of the six subjects were able to stop prophylaxis, with significant improvement in quality of life; the other three subjects remain on prophylaxis but at extended treatment intervals of once every 10-14 days.

The high-dose cohort was expanded in 2012 with four new subjects recruited. The aim was to determine if a consistent level of gene transfer would be observed; whether perturbation of liver enzymes would occur in all subjects treated at the high dose level; whether early treatment with steroids would reduce the level of transaminitis and preserve stable expression of FIX; and whether all high-dose subjects should receive prophylactic steroids between 6-12 weeks after gene transfer. There was evidence of vector-mediated human FIX expression in all 10 subjects with follow-up between 1 to 4.5 years. FIX expression was consistent at the high dose level of about 5%. Four subjects were able to stop prophylaxis, with significant improvement in quality of life and no spontaneous bleeds.

As for hemophilia A, bioengineering of FVIII has resulted in a potent HLP-codop-hFVIII-V3 expression cassette that is efficiently packaged into AAV vectors. Dose finding studies have suggested that doses that were effective in hemophilia B will produce a therapeutic level of FVIII in hemophilia A. A gene therapy

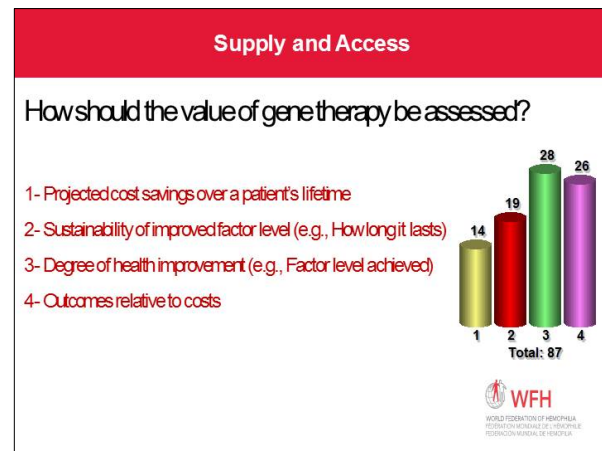
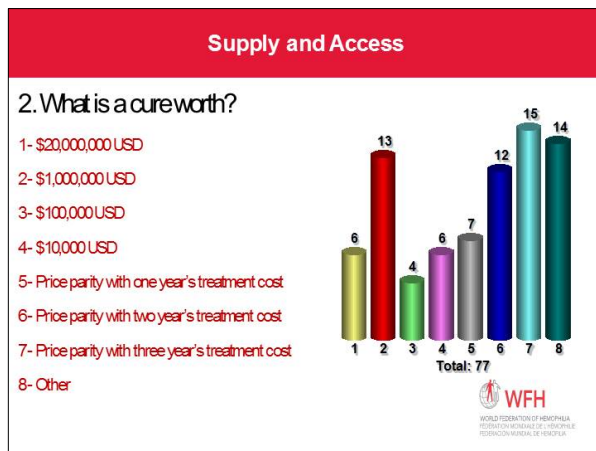
trial for hemophilia A using AAV was initiated in Fall 2015.

AAV-mediated gene therapy has the potential to be a new paradigm in treatment for hemophilia. A single administration of AAV vector can result in safe and consistent long-term expression of transgene (over five years), reduction in spontaneous bleeding episodes, reduction in clotting factor usage, and improvement in quality of life. Commercialization of this approach will require improved vector production, demonstrated efficacy in children, and elimination of immune response to AAV-mediated gene transfer.

Discussion

There have now been about 40-50 patients with hemophilia treated with gene therapy, noted Dr. Lillicrap. Patients in the UCL trials have had heterogeneity of responses including hemorrhage, and patients in the Padua study also showed significant variances in response. Is it possible to be more predictive? This is a big issue being investigated, said Dr. Tuddenham. Variability in response was also seen in preclinical studies on mouse and monkey models. Most patients have pre-existing antibody levels present in their bloodstream, said Dr. Tuddenham. Select patients are screened for antibodies to AAV8 or AAV5 and there is an incidence of previous exposure or possible cross-reaction. Some patients may have higher antibody levels than others. The researchers are now developing a model for in vivo antibody studies.

Dr. Lillicrap noted that a key issue not often discussed is how much gene therapy for hemophilia will cost, whether it is a lifetime cure, and how the hemophilia community will be able to afford it. The audience was polled for their views.



Gene therapy for hemophilia – future scenarios for cost, capacity and impact on FVIII therapy

GLENN PIERCE, VICE PRESIDENT, WFH EXECUTIVE COMMITTEE

MARK SKINNER, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA USA (WFH USA); WFH PAST PRESIDENT

Dr. Glenn Pierce gave an overview of advancements and challenges in gene therapy for hemophilia, and some different scenarios for how to estimate the costs and impacts of gene therapy. Scientists have been thinking of gene therapy seriously for hemophilia since about 1990, when the first gene therapy experiments were done in severe combined immunodeficiency disease (SCID). Risk of immunogenicity of

the delivered gene product was initially a concern in the 1990s but has proven not to be the case for hemophilia and other patients exposed to recombinant preparations. However, the challenge of preparing consistent, high quality adenovirus vector (AAV) lots has persisted over the past 15 years, along with new lentiviral vectors which require assessment for longterm safety. About 50 per cent of the population has anti-AAV antibodies (neutralizing antibodies in their plasma that prevent the AAV vector from reaching the target) and cannot be treated with AAV gene therapy. There are currently no standardized assays to measure vectors and anti-AAV antibodies.

Moving forward, a new vector is needed which can target the whole patient population, along with scaled up manufacturing of vectors, and gene editing to fix the defect with or without stem cells. A number of promising preclinical gene therapy projects are now underway using AAV vector modifications to optimize and increase protein expression and the longevity of drug benefits. However, certain patients are excluded from AAV gene therapy trials, such as children and adolescents under 18, hemophilia A patients with FVIII levels above 1%, hemophilia B patients with FIX levels above 2%, HCV RNA positive patients, patients with inhibitors, and patients with positive AAV serotype antibody. Hemophilia B responses were inconsistent but positive in some cases, with some patients converting to moderate or mild hemophilia B; hemophilia A clinical trials have now begun.

The definition of “cure” is also important (e.g., less acute bleeding with less time per week below 1% factor levels, less time below 5% factor levels, no bleeding with factor levels above 15% or 50%). This is particularly important for assessing the value of therapy for individual patients.

Determining a fair price for gene therapy depends on the drug outcomes and value-based pricing. Other considerations include return on investment, development costs (time and money), manufacturing costs, size of treatable population, longevity of treatment, and degree of independence from factor therapy requirements. In terms of time, development of a new drug takes about 12-13 years from beginning to end. In terms of monetary costs, drug development prices have escalated since the 1970s—prices for research and development of new drugs have risen from \$179 million in year 2000 to \$2.5 billion in the early 2010s. “The initial costs of gene therapy production will be very high—but the value of curing compared to treating hemophilia is also very high,” Dr. Pierce said. The cost of gene therapy should be calculated on the basis of value-based pricing. Key parameters for assessing cost include effectiveness, efficacy, safety, cost savings to the healthcare system, and quality of life improvements.

Gene therapy has enormous potential for the hemophilia world including developing countries, said Mark Skinner. The affordability of gene therapy is a key challenge, and payers must be persuaded to take a longitudinal perspective of the cost of gene therapy that reflects the value and benefits that the hemophilia community sees in gene therapy. “The value of a drug intervention is not just how much it costs but also the impact of those costs on the outcomes of the patients. In addition to patient health outcomes such as decreased morbidity and joint bleeds, these values include quality aspects such as educational attainment and the ability to maintain employment,” Mr. Skinner said.

As the hemophilia community considers outcome measures and longitudinal tools to track important treatment outcomes, it is important to work with drug developers now to build outcome measures that payers and others will use to assess the drug price down the road and to persuade them to take a more holistic approach. Measuring the total costs over a patient’s entire care cycle and weighing them against outcomes will enable truly structural cost reduction.

With new pricing regimes it is important to define the outcomes or value-based pricing systems and risk-sharing agreements, such as pay for performance, managed entry, conditional reimbursement, or

coverage with evidence development and generation. Outcomes and real world evidence are going to be fundamental to moving forward.

WFH Research Program: Outcomes and future directions – panel discussion

CHAIR: DAVID LILICRAP, CHAIR, WFH RESEARCH COMMITTEE

Dr. David Lillicrap gave an overview of the WFH Research Program to set the framework for the panel discussion with fellow members of the WFH Research Committee: Mike Soucie, Centers for Disease Control, USA; Susan Cutler, Penn Comprehensive Hemophilia and Thrombosis Center, USA; Deon York, Haemophilia Foundation New Zealand; and WFH VP Marijke van den Berg.

The WFH Research Program was launched in 2012 with a focus on clinical research and epidemiological research. The Clinical Research Grants Program was initiated within its remit, with the first competition held in August 2013; eight clinical research grants have been awarded to date. The Epidemiology Research Program, referred to as the World Bleeding Disorder Registry (WBDR), was subsequently launched with a focus on individual anonymized patient outcomes and aggregate data from multiple sites around the world.

Panelists were asked to comment a series of questions on current and upcoming research issues related to treatment of hemophilia and other inherited bleeding disorders.

Multidisciplinary research projects are well suited to the inherited bleeding disorder community. How can WFH encourage more involvement of healthcare professionals with less experience in conducting research?

Communications such as requests for proposals should emphasize the need for multidisciplinary healthcare professionals especially in the areas of nursing, psychosocial care, physiotherapy, and genetic counselling as well as the need for evidence-based research, said Dr. Susan Cutler. It is important to encourage new researchers in developed or developing countries alike to come on board bleeding disorder research initiatives for research experience with experienced investigators or institutions. Dr. Marijke van den Berg said outcomes research and the generation of corroborative evidence require a multi-year commitment. The current period for WFH research projects is about two years, which is a relatively small period to prepare a proposal, get multiple treatment centres involved, and collect the data. The WFH Research Committee is looking into the limitations of the current framework and its ability to involve the type of patients needed to improve the current knowledge.

In an environment where patient-oriented research is increasingly being encouraged, how should WFH integrate this theme into its research agenda?

It is important to provide meaningful feedback (e.g., time series of prophylactic and on-demand infusions and occurrence of bleeds) not only to clinicians but to patients as well in order to encourage their participation in patient-reported data and outcomes research, said Deon York. It is also important to have strategies to mitigate having multiple individuals inputting data into a data system.

A number of tools for logging infusions are available but their level of usage have depended largely on how valuable patients see them in terms of their own care, said Dr. Mike Soucie. It would be helpful for the WFH to emphasize that providers of education must spend time showing patients how to use the tools and how effective they are towards their care—this would go a long way to improving both the amount

and quality of data for patient-oriented research. In addition, it is important to have a record of bleeding events, which is very important for understanding treatment outcomes, Dr. Alok Srivastava said. There needs to be a way to get bleeds recorded consistently so that data from such studies can be comparable.

Dental evidence in hemophilia has not been prioritized, said Dr. Alison Dougall. There is almost no evidence, except for good evidence on provisional care for patients on anticoagulants. It is important to collaborate to develop evidence-based dental practices and guidelines.

The research capabilities of healthcare professionals around the world will vary markedly, depending upon resource availability. How should this factor be taken into account in developing the WFH research agenda?

The WFH could leverage prior twinning partnerships to re-initiate interest in joint collaborations between developed and developing countries, where proper diagnosis and demographic data collection are already in place on a small scale, said Dr. Cutler. It would be useful for WFH to clearly outline the steps for patient-oriented research, said Mr. York.

Dr. Magdy El Ekiaby said it would be valuable to have a mentorship program for guiding new researchers on how to conduct proper research, the benefits of which would include the ability to leverage research in developing countries and make sure that methodologies and data are correct.

WFH Epidemiological Research Program

ALOK SRIVASTAVA, CHAIR, WFH EPIDEMIOLOGICAL RESEARCH PROGRAM

Dr. Alok Srivastava gave an overview of the WFH Epidemiological Research Program (ERP), created to help support clinical research that will provide evidence-based data for the management of hemophilia. The objective of the Epidemiological Research Program is to collect individual patient data on demographic and clinical profile, treatment and outcomes and create a World Bleeding Disorders Registry, which would serve as a platform for directed epidemiological and outcomes research. The primary data sources for epidemiological research are clinical care documentation from hemophilia treatment centres and cohort-based data collection from national and regional registries and collaborative group data. The program aims to use more focused groups (e.g., selected centres/countries) to collect cross-sectional or longitudinal data from regular clinical practice to broadly address safety and efficacy issues.

The WFH Research Committee has identified 11 important domains related to quality clinical care and epidemiological research: baseline information, baseline update, treatment, inhibitor, bleeding, joint status and pain, co-morbidities, dental care, physical activities, social participation, and quality of life. Observational data will be collected among patients with hemophilia A and B who are being treated at one of the participating hemophilia treatment centres, using a universal case record form (U-CRF) that reflects the recommended requirements for documentation of the diagnosis, treatment provided, and outcomes on an annual basis for each patient. Participation in the program will be voluntary. Participating centres will have the option to use the registry infrastructure to collect data for their own clinical or research purposes, and will be invited to share their data in aggregate anonymized form with the WBDR. When adequate aggregate data is available, the WFH will produce summary reports on current practices, trends, and outcomes in hemophilia care worldwide, for example, disease severity, inhibitor development, annual bleed rate, type of factor replacement therapy, and joint outcomes. In

addition, the observational data in the WBDR will be made available upon request to researchers from participating centres who wish to design additional studies.

There are several challenges ahead for the WFH Epidemiological Research Program. First, getting community acceptance—convincing HTCs on the need for data documentation and convincing funders to provide centres with the resources to do so. Second, establishing a governance model for data storage, access, ownership, analysis, and publications; there are good existing models. Finally, resources and funds are needed for initial program management and implementation, and development of infrastructure for longterm systematic data collection. The WFH is working to create internal resources to move this program forward.

Discussion

Dr. Magdy El Ekiaby asked how countries that already collect data for national registries and other databases can contribute to the epidemiological research initiative. Dr. Srivastava replied that a key issue is to not duplicate registries. There are ways to handle such challenges, such as agreements on data sharing and transfer.

Dr. Mike Soucie said it's taken a long time to develop a hemophilia surveillance system in the U.S. The World Bleeding Disorders Registry will require substantial WFH resources and outreach to convince people to contribute to the registry, and willingness and commitment by clinicians and treatment centres to collect the data. It is important to figure out how to take advantage of existing infrastructure to operationalize the registry, and ensure that partners will not be expected to fill in the same data they are currently already enter into other systems and databases. Dr. Alfonso Iorio noted that there are several existing universal patient identifiers that are privacy compliant and can be used across different studies and registries, however, enforcing their use is difficult.

Updates from WFH clinical research grant recipients

Quantifying foot biomechanics in children with hemophilia

SÉBASTIEN LOBET, PT, PHD, CLINIQUES UNIVERSITAIRES SAINT-LUC, UNIVERSITÉ CATHOLIQUE DE LOUVAIN, BELGIUM

Dr. Sébastien Lobet described clinical research findings to date from a study on foot biomechanics in children with hemophilia, conducted with Dr. Kevin Deschamps of UZ Leuven University as 2013 WFH research grant recipients. The ankle joint is a very problematic joint; despite frequent and adequate prophylaxis, children with hemophilia continue to bleed into the ankle due to multifactorial causes. Once a bleed into the ankle occurs, a biomedical change is triggered in the joint and may cause multiple bleeds and it becomes a target joint.

The definition of joint function is very broad and can include assessment of gait, muscle strength, range of motion, etc. Determination of the functional deficits is paramount to assess the evolution of the joint disease, develop clinical treatment strategies, and quantify the effectiveness of rehabilitation programs. There are a number of ways to assess the musculoskeletal status of patients with hemophilia such as the WHO International Classification of Functioning, Disability and Health (ICF) and the Functional Independence Score in Hemophilia (FISH).

The aim of the Belgium study was to use three-dimensional analysis to assess functional performance in

children with hemophilia and establish a possible correlation with structural damage, and determine whether functional tests could be an alternative to radiological assessment and raise the sensitivity of these functional tools. More than 20 different movements were assessed. In addition, all patients had MRIs to assess ankle structural impairment and damage, i.e., soft tissue changes (hemarthrosis, synovial hypertrophy, hemosiderin), osteochondral changes (surface erosions, subchondral cysts, cartilage degradation). Of 37 patients assessed by MRI, 18 patients had no structural damage; 7 patients had bilateral transverse tarsal joint or subtalar joint impairment. There were 8 patient with osteochondral changes and 9 patients with soft tissue changes.

Preliminary results on ankle muscle strength found no ankle muscle strength deficit in children with hemophilia with evidence of structural damage—this suggests the presence of a possible structural delay between joint structural impairments and repercussion on muscle function. The study continues to investigate several aspects of musculoskeletal properties of the calf muscle—visco-elastic properties, muscle recruitment during gait, foot kinetics and kinematics, plantar pressure, and balance.

The study is supported by funds from the 2014 WFH Clinical Research Grant, Bayer Hemophilia Award Program in 2012 (Dr. Sébastien Lobet), and Pfizer Aspire Grant 2013 (Dr. Kevin Deschamps).

Joint distraction in the treatment of hemophilic ankle arthropathy

LIZE VAN VULPEN, MD, PHD STUDENT, RHEUMATOLOGY AND CLINICAL IMMUNOLOGY, VAN CREVELD CLINIC, UTRECHT UNIVERSITY MEDICAL CENTRE, UTRECHT, THE NETHERLANDS

Dr. Lize van Vulpen presented preliminary results from a prospective study on joint distraction in the treatment of hemophilic ankle arthropathy conducted at the van Creveld Clinic. Joint distraction is a surgical procedure in which the two bony ends of a joint are gradually separated to a certain extent for a certain period of time (5mm for 10 weeks for ankles). It has been found to improve joint damage in osteoarthritis. It has been used to treat equine deformities by actively repositioning the joint, and prevent damage due to compression of the joint cartilage. A 2005 study found prolonged clinical benefit and longterm improvement in pain and disability, and preservation of range of motion and flexion in 73 per cent of patients even 10 years following ankle distraction.

There are several indications for which distraction can be performed safely in hemophilia patients: contractures, arthrodesis of infected joints, and treatment of open fractures. In its prospective pilot study, the van Creveld Clinic investigated the use of ankle distraction for 10 weeks in patients with ankle arthropathy, ages 18 to 55 years, with three years of follow-up. The study enrolled six patients with hemophilia A or B treated on demand or with prophylaxis. Before surgery, a bolus of factor concentrate was infused. After surgery, continuous factor infusion was administered for one week, at which point the patient was discharged and put on intensified prophylaxis for one week. After day 14, the regular treatment protocol resumed, then a single bolus was administered before removal of the distraction frame. In terms of adverse events, there was no bleeding from insertion of the frame; four patients had skin pin site infection which were treated with oral antibiotics and one patient received antibiotics for knee pain.

Preliminary results indicate that joint distraction is a safe procedure in patients with hemophilia when used with clotting factor replacement therapy. One year after distraction, all patients showed improvement in functionality (assessed through standardized walking tests—figure eight performance, figure eight maximum speed, 50m walk, 6-minute walking distance). MRIs at the one-year follow-up showed structural improvements in some patients including increased joint space and a reduction in bone

cysts and edema. Patients also had a clear reduction in pain and improvement of functionality with preservation of joint motion. Joint distraction is therefore a promising treatment to postpone ankle arthrodesis in young patients with hemophilic arthropathy.

This research is supported by a WFH Clinical Research Grant and an unrestricted grant from CSL Behring.

Manufacturers Updates

CHAIR: ALOK SRIVASTAVA, CHAIR, WFH EPIDEMIOLOGICAL RESEARCH PROGRAM

Sobi: Extended half-life recombinant Fc-fusion factors: Potential to advance standard of care

Dr. Geoffrey McDonough, President and CEO of Sobi AB, described safety and efficacy results from their phase 3 clinical trial of recombinant FVIII Fc-fusion factor protein (rFVIII-Fc), a novel therapy called Eloctate[®] approved by the U.S. Food and Drug Administration and Health Canada in 2014 and manufactured in partnership with Biogen. rFVIII-Fc is produced in a human cell line, potentially minimizing immunogenicity risks. It provides significantly increased time to 1 or 3% above baseline factor level through an extended half-life by 50 per cent (1.5-fold). The clinical trial had three arms: individualized prophylaxis, weekly prophylaxis, and episodic treatment. Patients showed a significant reduction in annualized bleeding rates (ABR). Patients in the individualized prophylaxis arm achieved significantly lower median ABR, from six bleeds pre-study to no bleeds by the end of the clinical trial; 98.8% of these patients had a decrease in number of injections per week. Overall, 87.3 per cent of bleeding episodes were resolved with one injection, and 97.8 per cent with two or fewer injections. No inhibitors were observed and other adverse events were consistent with those expected in the general hemophilia population. In an initiative aimed at providing a more predictable, sustained supply of factor VIII and IX for people with hemophilia in the developing world, Biogen and Sobi will donate 1 billion IU of rFVIII-Fc and rFIX-Fc over the next 10 years to the WFH Humanitarian Aid Program from their commercial supply.

Kedrion: Growing as a global company

Dr. Garrett Bergman, Senior Director, Medical Affairs, at Kedrion Biopharma, described three therapies in their pipeline: a new generation immunoglobulin for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy, which will begin a phase 3 pivotal trial in 2016; a plasma-derived FV concentrate, which has solvent-detergent treatment and nanofiltration steps within the manufacturing process; and a plasminogen concentrate for ophthalmic conditions and congenital plasminogen deficiency, now in phase 2/3 clinical trial, with the aim to obtain FDA licensing in 2017.

Grifols: The natural protection of FVIII by VWF against inhibitors

Dr. Juan Ignacio Jorquera, Vice President of Grifols' Global Research and Development Bioscience Industrial Group, gave an overview of in vitro and in vivo studies on how von Willebrand factor (VWF) provides natural protection of FVIII against inhibitors. The presence of VWF in the natural FVIII/VWF complex affects FVIII in several ways. It increases circulating half-life, protects from premature inactivation, obscures functional binding sites important to cofactor function, and reduces its immunogenicity at least in vitro and in animal models of hemophilia. Plasma-derived FVIII/VWF products behave similarly to normal plasma in the presence of FVIII inhibitors. Concentrates of isolated FVIII (without VWF; plasma-derived or recombinant) show higher Bethesda titers even after being pre-

mixed with VWF before the assay.

In vitro results suggest that there may be structural and/or functional differences between the natural FVIII/VWF complex and the FVIII/VWF compound formed from the isolated proteins. In vivo studies found VWF-containing FVIII concentrates are more effective to restore FVIII circulating levels. FVIII recovery was higher for the natural VWF-containing FVIII concentrate (pdFVIII/VWF) when compared to concentrates of isolated FVIII (pdFVIII and rFVIII), except in the presence of very high inhibitor titers. The in vivo results also suggest that this protection would be higher in natural plasma-derived FVIII/VWF complex than in the complex of FVIII/ VWF formed from the isolated proteins. This deserves further analysis. Studies in a murine model are ongoing. These results strongly support the recommendation to perform a Bethesda assay with different therapeutic concentrates prior to treatment of inhibitor patients. Globally, the results suggest that there may be structural and/or functional differences between the natural FVIII/VWF complex and the FVIII/VWF compound formed from the isolated proteins.

Bio Products Laboratory: Pharmacokinetics, safety and efficacy of Coagadex®

Dr. Eric Wolford, Vice President, Global Medical, at Bio Products Laboratory (BPL), gave an overview of the pharmacokinetics, safety and efficacy of Coagadex®, a new high-purity factor X concentrate for patients with inherited factor X deficiency. Clinical study data currently are under review by the FDA and the EMA. Coagadex® involves three processing steps to remove or inactivate viruses: solvent/detergent treatment targeted to enveloped viruses, a virus filtration step to remove small viruses including non-enveloped viruses, and terminal dry heat-treatment at 80°C for 72 hours in the final container to inactivate enveloped and non-enveloped viruses.

BPL has conducted two studies to evaluate the use of Coagadex® in patients with inherited FX deficiency. The TEN01 clinical trial focuses on efficacy, safety and pharmacokinetics, while the TEN03 trial focuses on the use of Coagadex® in patients undergoing surgery. A third study, TEN02, investigating twice weekly prophylaxis in pediatric patients is underway in the UK. Pharmacokinetic analysis demonstrated that Coagadex® has a mean incremental recovery of 2.0 IU/dL per IU/kg and a mean half-life of approximately 30 hours. Data demonstrate that Coagadex® is safe and efficacious in on-demand treatment of bleeds and short-term preventative therapy in subjects with moderate or severe FX deficiency at a nominal dose of 25 IU/kg, and effective in maintaining hemostasis in subjects undergoing surgical procedures.

Meeting unmet needs in hematological disorders

Baxalta has explored multiple approaches to develop longer-acting rFVIII therapies, said Dr. Anne Prenner, VP Clinical Research and Global Therapeutic Area Head Hematology at Baxalta. Each approach builds on the Advate® platform of full-length, plasma/albumin-free rFVIII therapy. Phase 1/2/3 pivotal studies have been completed for the lead compound, BAX 855, a pegylated full-length rFVIII. Additional research on other approaches to extend rFVIII half-life is ongoing, including a second generation candidate, BAX 826, a polysialylated full-length rFVIII. Results from a phase 3 clinical trial of BAX 855 showed a 95 per cent reduction in median annualized bleed rate for twice-weekly prophylactic regimen, and 96 per cent of bleeds were controlled with one or two infusions. No subjects developed inhibitors or treatment-related serious adverse events. A prospective, randomized, multi-centre clinical study is underway comparing the safety and efficacy of BAX 855 following pharmacokinetic-guided prophylaxis targeting two different FVIII trough levels in patients with severe hemophilia A.

Obizur is another therapy under clinical development. A prospective, non-randomized, open-label study has evaluated the proportion of serious bleeding events responsive to Obizur therapy 24 hours after treatment initiation, as well as safety and pharmacokinetics, in subjects with acquired hemophilia A. All subjects showed a positive response at 24 hours. Patients achieved high FVIII activity with no related thrombotic events reported and demonstrated ability to monitor FVIII activity and titrate dose and regimen to achieve clinically relevant FVIII activity levels. There were no related serious adverse events nor thrombotic events, thrombocytopenia or hypersensitivity reactions.

Vonvendi, Baxalta's recombinant VWF concentrate (rVWF), has completed its pivotal study with results showing a 100% treatment success rate; bleed resolution were rated excellent or good in all subjects, with bleeds resolved with one infusion for mild VWD and two for severe VWD. Vonvendi was safe and well tolerated, with no thrombotic events, allergic reactions and antibody development to VWF.

Baxalta is also developing recombinant ADAMTS13 (BAX 930) for the treatment of hereditary thrombotic thrombocytopenic purpura (TTP), which may eliminate the adverse event profile of plasma infusions, and may allow for full normalization of TTP-related events.

Bayer: The future of hemophilia A care

Dr. Nikolaus Mueller, Head of Pipeline and Innovation, Hematology at Bayer HealthCare, described several new therapies being developed.

BAY 81-8973 is a new, full-length, unmodified rFVIII product with the same amino acid sequence as Kogenate FS/Bayer, but manufactured using an improved cell bank compared to Kogenate FS/Bayer; the inclusion of the gene for HSP70, which inhibits apoptosis, may increase proper folding of the FVIII protein and expression. No human- or animal-derived materials are added to the cell culture, purification, or formulation processes. A new viral filtration step has been added, which uses 20 nm pore-size viral filter capsules capable of removing even small non-enveloped viruses and potential protein aggregates. BAY 81-8973 has consistent glycosylation and increased sialylation relative to Kogenate FS/Bayer. It offers proven efficacy and dosing as few as twice weekly.

BAY 94-9027 is a site-specific pegylated B-domain-deleted recombinant FVIII, shown in a phase 1 study to have a half-life of about 19 hours, decrease the frequency of injections and need for central venous access devices and device care, and prevent bleeding at dose intervals up to every 7 days. It has demonstrated reduced FVIII immunogenicity in animals in vivo and humans in vitro. Bayer is also exploring therapies with alternative targets in the coagulation cascade, including anti-TFPI and AAV-based gene therapy.

Pfizer: Hematology pipeline – Rare disease development program

Dr. Marcus Carr, Vice President of Clinical Hematology at Pfizer, described a number of therapies in the pipeline. In hemophilia A, a phase 3 clinical trial on an albumin-free, B domain-deleted recombinant FVIII, Moroctocog Alfa (AF-CC), in children with hemophilia A is comparing prophylaxis to on-demand therapy, using the annualized bleed rate as the primary endpoint for testing. AF-CC has been approved by the FDA for licensing in the U.S. In hemophilia B, Pfizer is collaborating with Spark Therapeutics on gene therapy for hemophilia B using a bioengineered adeno-associated viral vector with high-activity FIX, SPK-9001. A phase 1/2 dose-escalation studies finds a number of participants experiencing drug-related adverse events as assessed by physical exam, vital signs, standard clinical labs, and Bethesda assay for FIX inhibitor. Research is also underway on an alternative hemostatic pathway for the treatment of

hemophilia A and B inhibitors, with a phase 1 study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of the tissue factor pathway inhibitor, PF-05230907.

Novo Nordisk: N8-GP and N9-GP update

Dr. Karin Knobe, Vice President Hemophilia Medical and Science at Novo Nordisk, gave an overview of several new therapies based on glycopegylation currently under development. In hemophilia A, a phase 3 trial of the new recombinant FVIII therapy, N8-GP, in previously treated patients (PTPs) under 12 years of age showed a single dose has a half-life of 18.3 hours and 96 per cent of bleeds were treated with 1-2 injections. No safety concerns were identified; one patient developed an FVIII inhibitor after 93 exposure days. A phase 3 trial in PTPs over 12 years of age showed that 80 per cent of bleeds were treated with 1-2 injections. No patients developed inhibitors. In hemophilia B, a phase 3 trial of the new recombinant FIX therapy, N8-GP, in PTPs over 12 years of age showed a half-life of 110 hours and a 92 per cent success rate in treatment of bleeds. A phase 3 trial in PTPs under 12 years of age showed a half-life of 70-76 hours and a 93 per cent success rate in treatment of bleeds. There were no safety concerns identified, nor inhibitor development.

Glycopegylation technology offers the possibility of significantly extending the half-life of native coagulation factors. Increased knowledge about assay performance ensures accurate monitoring of long-acting products. Higher trough levels support the potential for improved outcomes, as shown by the reduction in the number of target joints in patients with hemophilia B.

Octapharma: Emerging data from ongoing global studies with Nuwiq®

Sylvia Werner, Director of Clinical Operations at Octapharma USA, presented data from ongoing studies with Nuwiq®, the first B-domain deleted recombinant factor VIII derived from a human cell-line. Nuwiq® has demonstrated excellent safety, tolerability and efficacy in children and adults in large clinical trials, and significantly higher VWF binding affinity than existing full-length rFVIII. It has been approved in Europe, Australia, Canada, and the United States. A phase 3 trial is investigating immunogenicity, efficacy and safety the efficacy of Nuwiq® during prophylactic treatment, treatment of breakthrough bleeds, and in surgical prophylaxis, as well as immunogenicity, safety and tolerability.

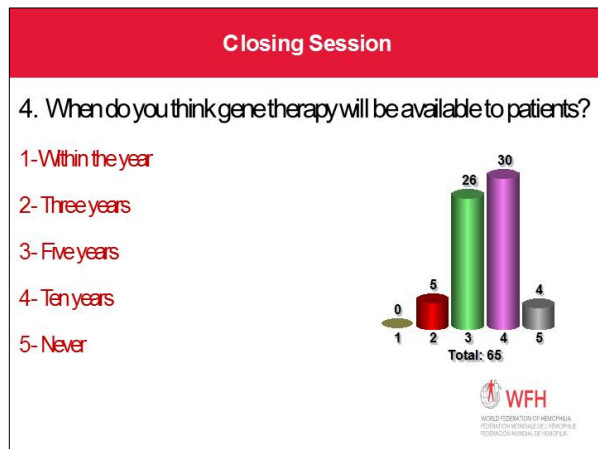
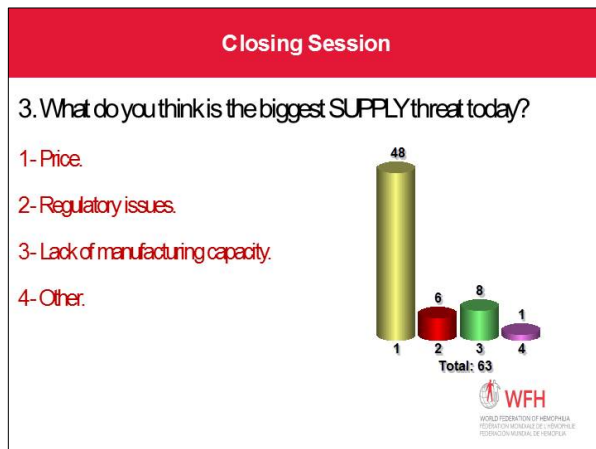
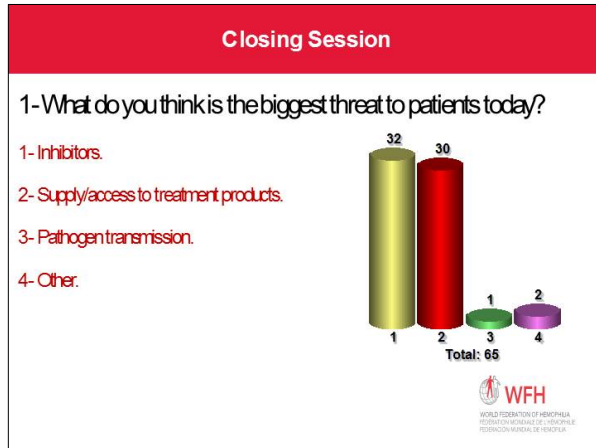
CSL Behring: Innovations in coagulation – rVIII-SingleChain, rFIX-FP and rFVIIa-FP

Dr. Debbie Bensen-Kennedy, Therapeutic Area Head of Coagulation at CSL Behring, presented clinical data on three recombinant hemophilia therapies: a recombinant single-chain FVIII molecule (rVIII-SingleChain) and recombinant FIX and FVIIa fusion proteins (rFIXFP and rFVIIaFP). The rVIII-SingleChain is a B domain-deleted molecule. Phase 1, 2 and 3 studies have been completed. Clinical data showed rVIII-SingleChain had more favourable pharmacokinetic properties than full-length recombinant FVIII, with lower clearance, greater area under the curve, and longer half-life. It was well tolerated locally and systemically, and showed excellent efficacy in on-demand, prophylaxis and for surgical procedures. Extension studies on adults, children, pediatric patients, and PUPs are ongoing.

rFIXFP and rFVIIaFP are based on albumin fusion technology to extend the half-life of the circulating molecules. Phase 1, 2 and 3 studies have been completed and extension studies are underway. Clinical data on rFIXFP showed a significantly improved pharmacokinetic profile compared to currently available FIX products and a 100% improvement in annualized spontaneous bleeding rates. There is no evidence of inhibitor development against FIX, nor antibodies against rFIXFP. CSL Behring is also developing rFVIIa-FP for the treatment of patients with hemophilia who have FVIII or FIX inhibitors.

CLOSING

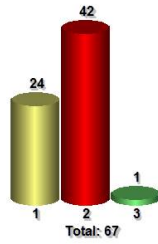
WFH Executive Director Alain Baumann thanked the Global Forum speakers for their presentations and participants for their attendance and involvement in the discussions. He thanked WFH staff for their work organizing the 9th WFH Global Forum. The audience was polled again on the series of questions asked at the start of the Global Forum to obtain a sense of how perceptions and understanding may have changed over the course of the meeting.



Closing Session

5. Did this Global Forum . .

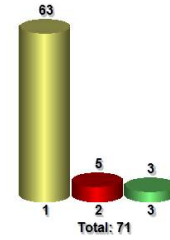
- 1- Exceed your expectations?
- 2- Meet your expectations?
- 3- Not meet your expectations?



Closing Session

6. Do you agree with the WFH's decision to combine the two meetings?

- 1- Yes
- 2- No
- 3- I don't know



ACRONYMS AND ABBREVIATIONS

AAV	Adeno-associated viral vector
ABR	Annualized bleeding rate
ATIII	Antithrombin III
BCA	Blood Centers of America
CDC	U.S. Centers for Disease Control
DDAVP	Demopressin acetate
DNA	Deoxyribonucleic acid
EMA	European Medicines Agency
ERP	WFH Epidemiological Research Program
FDA	U.S. Food and Drug Administration
FFP	Fresh frozen plasma
FISH	Functional independence score in hemophilia
FIX	Factor IX
FIXa	Activated factor IX
FV	Factor V
FVIII	Factor VIII
FVIIIa	Activated factor VIIIa
FX	Factor X
HBV	Hepatitis B
HCV	Hepatitis C
Hemo-QoL	Hemophilia quality of life
HEV	Hepatitis E
HIRS	U.S. Hemophilia Inhibitor Research Study
HIV	Human immunodeficiency virus
HTC	Hemophilia treatment centre
ICER	Incremental cost-effectiveness ratio
ICF	WHO International Classification of Functioning, Disability and Health
ID NAT	Individual nucleic acid test
iPSC	Induced pluripotent stem cells
ITI	Immune tolerance induction therapy
IU	International unit
IVIG	Intravenous immunoglobulins
MSM	Men who have sex with men
MRI	Magnetic resonance imaging
pdFVIII	Plasma-derived factor VIII
PPTA	Plasma Protein Therapeutics Association
QALY	Quality adjusted life year
QoL	Quality of life
rFVIII _{FC}	Recombinant factor VIII Fc-fusion factor protein
rFIX _{FC}	Recombinant factor VIII Fc fusion protein
rFIX _{FP}	Recombinant factor IX protein
rFVIIa _{FP}	Recombinant factor VIIa fusion protein
rFVIII	Recombinant factor VIII
rFVIII _{FC}	Recombinant factor VIII Fc fusion protein
RNA	Ribonucleic acid
rVWF	Recombinant von Willebrand factor concentrate
SCID	Severe combined immunodeficiency disease
TFPI	Tissue factor pathway inhibitor

TPSSA	WFH Treatment Product Safety, Supply and Access Committee
TTP	Thrombotic thrombocytopenic purpura
U-CRF	Universal case record form
vCJD	variant Creutzfeldt-Jakob disease
VWD	von Willebrand disease
VWF	von Willebrand factor
WBDR	World Bleeding Disorder Registry
WFH	World Federation of Hemophilia

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