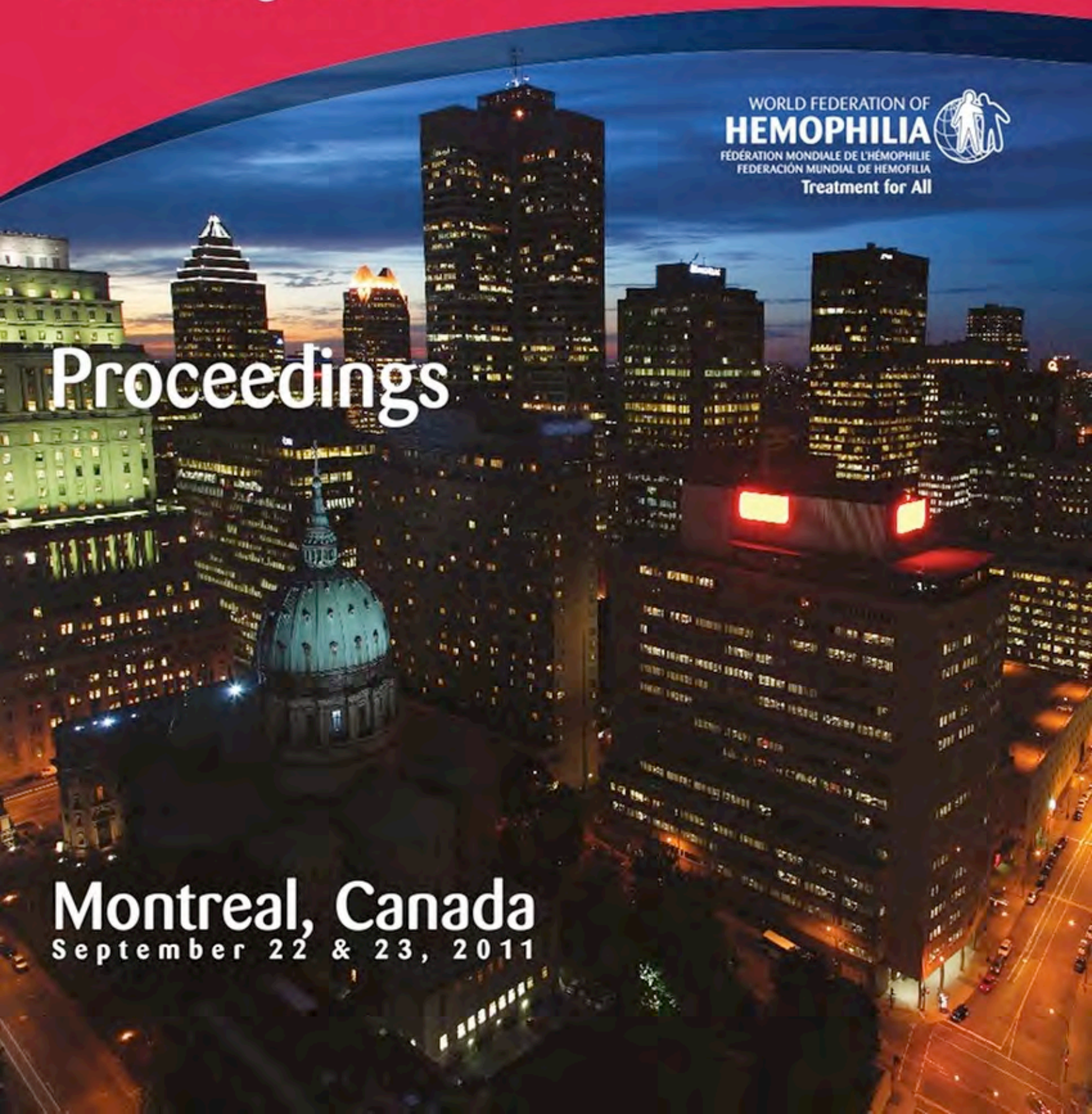
THE WORLD FEDERATION OF HEMOPHILIA'S

Seventh Global Forum

on the Safety and Supply of Treatment Products for Bleeding Disorders



WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA
Treatment for All

Proceedings

Montreal, Canada

September 22 & 23, 2011

The Proceedings of the World Federation of Hemophilia's Seventh Global Forum on the Safety and Supply of Treatment for Bleeding Disorders

Please note: This material is intended for general information only. The World Federation of Hemophilia does not endorse particular treatment products or manufacturers; any reference to a product name is not an endorsement by the WFH. The WFH is not a regulatory agency and cannot make recommendations relating to safety of manufacturing of specific blood products. For recommendations of a particular product, the regulatory authority in a particular country must make these judgments based on domestic legislation, national health policies, and clinical best practices.

The WFH does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Any treatment must be designed according to the needs of the individual and the resources available.

Published by the World Federation of Hemophilia

Additional copies are also available from the WFH at:
World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montreal, Quebec H3G 1T7
CANADA
Tel.: (514) 875-7944
Fax: (514) 875-8916
E-mail: wfh@wfh.org
Internet: www.wfh.org

Acknowledgements
The WFH gratefully acknowledges the financial contribution of Héma-Québec, Ministère des Relations Internationales du Québec (Quebec Ministry of International Relations) and Ministère de la Santé et des Services Sociaux Québec (Quebec Ministry of Health and Social Services), towards the 2011 Global Forum. Only through such support and partnerships can the World Federation of Hemophilia continue to provide important global interchange on issues related to blood product safety and supply.

The Proceedings of the World Federation of Hemophilia's Seventh Global Forum on the Safety and Supply of Treatment for Bleeding Disorders

September 22 & 23, 2011
Montreal, Canada

The World Federation of Hemophilia gratefully acknowledges
the sponsors of the 2011 WFH Global Forum:

Héma-Québec

Ministère des Relations Internationales du Québec
(Quebec Ministry of International Relations)

Ministère de la Santé et des Services Sociaux Québec
(Quebec Ministry of Health and Social Services)

Table of Contents

EXECUTIVE SUMMARY 1
DAY 1: SEPTEMBER 22, 2011 11
Welcome & Opening Remarks 11
Session 1: Perspectives on Risk 12
Risk-based decision-making for blood safety 12
Discussion 14
Advocacy to Revise Blood Donation Policies for MSM 15
MSM Donor Deferral 16
Efficacy of Testing Scenarios 18
Discussion 20
Session 2: Health Technology Assessment in Hemophilia 22
Hemophilia and Health Technology Assessment 24
Healthcare Reform and Healthcare Economics 26
Discussion 28
Session 3: Update on Inhibitors 29
How Do We Define A Clinically Relevant Inhibitor? 29
Update on Two Inhibitor Studies 30
Update on U.S. Hemophilia Inhibitor Research Study 33
Inhibitor Development in Mild/Moderate Hemophilia A 36
Discussion 37
Session 4: Clinical Trial Design 39
New Products for the Treatment of Hemophilia 39
ISTH Clinical Trial Design For Hemophilia Project Group 40
Discussion 42
Potency Assignment of Clotting Factor Concentrates 44
Discussion 46
DAY 2: SEPTEMBER 23, 2011 47
Session 5: Novel Technologies 47
Update on Haemophilia B Gene Transfer Study 47
Discussion 51
Solvent Detergent Cryoprecipitate – Clinical Experience Update 52
Discussion 55
Manufacturers' Updates 56
Pioneering Designs for Recombinant Coagulation Factors 56
Novel Treatment Options for Hemophilia 58
Biogen Idec Hemophilia Research Update 59
Manufacturing, Safety, and Efficacy of Recombinant FXIII 60
Session 6: Closing Panel 62
Closing Remarks 64
Glossary of Terms 65
List of Acronyms 69

NOTES

EXECUTIVE SUMMARY

Introduction

The World Federation of Hemophilia's Seventh Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders assembled over 140 international participants in Montreal, Canada, September 22–23, 2011. The meeting generated productive discussions and debates and brought forward a range of perspectives among stakeholders—people with bleeding disorders, hemophilia clinicians and researchers, ministry of health officials and regulators, and representatives from patient groups, blood agencies, not-for-profit fractionators, and industry.

It is now over 10 years since the first WFH Global Forum in April 2000, a groundbreaking meeting focused on issues surrounding the safety, availability, costs, and use of treatment products around the world, noted Claudia Black, WFH Executive Director. Held every two years, the global forums have helped build greater understanding of the diversity of circumstances and disparities in access to safe treatment globally and continue to generate important discussion and debate.

The WFH Global Forum presents the latest knowledge and developments in safety and supply of treatment products for bleeding disorders, said Mark W. Skinner, WFH President. A key goal is to try to improve consensus and understanding around the world on the most pertinent issues of the day. This year's program featured scientific and topical sessions on risk perspectives and blood donor deferral policies, health technology assessment and trends in healthcare decision-making, hemophilia inhibitors research, clinical trial design issues and harmonization of regulatory requirements, and novel technologies. The sessions and presentations were framed within three main themes:

- perspectives on risk including blood donor screening, viral testing and new infectious agents;
- achieving a safe and affordable supply including innovative global projects to improve supply, and changing trends in healthcare funding and regulatory policies;
- novel technologies including updates on gene transfer studies, longer-acting treatment products and other innovative product developments.

Perspectives on Risk

Vigilance of current and prospective risks to blood safety and blood recipients must be a continuous process given the experiences and lessons learned globally over the past 50 years of hemophilia treatment, said Dr. Magdy El Ekiaby, WFH Medical Executive. The blood system must pay close attention to the progress and developments in blood safety and supply, and respond to evolving public needs and new challenges. The best available science must be used in risk management decision-making. This session focused on three elements of blood safety: risk-based decision-making, blood donor deferral policies, and efficacy of blood testing and screening scenarios.

Dr. Judie Leach-Bennett, Executive Director of Research and Education at Canadian Blood Services, presented an overview of the International Consensus Conference on Risk-Based Decision-Making for Blood Safety held in October 2010, which produced a consensus statement on the necessary components of a comprehensive and robust blood safety approach. These include an integrated risk management framework that encompasses the "vein-to-vein" continuum from blood donor recruitment through patient monitoring; meaningful and ongoing engagement with stakeholders, particularly the patients who bear the risks; and transparent and precautionary decision-making based on the risk management principles of flexibility, proportionality, non-discrimination, and consistency. Finally, there must be a proactive risk management strategy that anticipates and prevents risks, constructed within the context of well-established ethical principles to ensure that the rights of both blood donors and patients are respected.

Nathan Schaefer, Director of Public Policy at the Gay Men's Health Crisis in New York City, discussed the U.S. blood donor deferral policy for men who have sex with men (MSM) and recent efforts to revisit the policy and questionnaire to end false perceptions and discrimination, while also increasing the safety and supply of blood donations. Policy change is needed to reflect actual risks and levels of risk (e.g., based on sexual activity and behaviours regardless of sexual orientation) and acknowledge the importance of increasing blood supply, he said.

A June 2011 recommendation by the U.S. Advisory Committee on Blood Safety and Availability (ACBSA) stated that current blood donor deferral policies are suboptimal, permitting high-risk donations while preventing some low-risk donations, but the currently available scientific data is inadequate to support change to a specific alternative policy. Until further evaluation, the committee recommended that the current indefinite deferral for any man who has had sex with another man even just once since 1977 not be changed at the present time. In July 2011, the U.S. Department of Health and Human Services announced that the Blood, Organ, Tissue and Safety work group has been charged to devise a workplan to review the policy; and additional studies will be done on donor understanding of the current standard questionnaire and whether MSM would be likely to comply with revised blood donor deferral criteria.

WFH President Mark Skinner noted that there have been significant social, cultural, and legal changes since MSM deferral policies were originally put in place in the mid-1980s, along with technological advances in the blood sector. A number of complex issues need to be balanced in the context of today's steadily increasing demand for blood products: donor recruitment and selection, blood supply, epidemiology, evolution of new pathogens, and risk management. Donor deferral criteria must put patient safety first and be based on large-scale epidemiological evidence and a behavioural-based system focusing on high-risk behaviours and activities. While testing and pathogen reduction technologies have advanced, they are not perfect; careful donor selection remains the cornerstone of a safe blood supply system. At the same time, a robust, systemic approach to hemovigilance is needed to track and counter known and emerging threats to the blood supply—donor screening, deferral and testing alone are insufficient to solve such complex problems. Changes to the U.S. MSM donor deferral policy would likely have impacts on the international supply of blood products, especially in countries that currently prohibit MSM blood donation. About 60% of the world's plasma comes from the United States.

Dr. Steven Kleinman of the Blood Systems Research Institute (USA) described an international multicentre study on efficacy of blood testing and screening scenarios, and the methods and technologies used to model mathematical risks and assess residual risks. The study's objectives are to classify HIV, hepatitis C, and hepatitis B infections into phases of infection and analyse them by geographic region; compare the efficacy of nucleic acid testing (NAT) and serology screening scenarios in donors; calculate residual risk and efficacy in each region; and compare the cost effectiveness of the different blood testing and screening scenarios.

The study involves centres in South Africa, the Mediterranean, Central and Northern Europe, Southeast Asia, the Pacific, and Egypt, which comprise the majority of countries that perform individual donor NAT. The first phase focused on transmission risk, efficacy (percentage of risk avoided), and cost effectiveness. Data collected included NAT and/or serology test results, and donor status (first time, repeat, or lapsed). More detailed data was collected upon pathogen detection. The prevalence of infectivity in first-time blood donors was found to be much higher than in lapsed donors, which in turn was much higher than in repeat donors. It is possible to remove almost all risk of infectivity from the blood supply using NAT and antibody testing—the question is whether countries are willing to pay for the individual donor NAT strategy, which is most effective but more costly, he said.

Achieving a Safe and Affordable Supply

This session focused on health technology assessments (HTAs) and comparative effectiveness studies of hemophilia care. Brian O'Mahony, Chief Executive of the Irish Haemophilia Society, spoke of the importance for health technology evaluators to properly assess the actual impacts, benefits and outcomes of hemophilia therapies, particularly prophylaxis. It is well established that early prophylaxis can decrease inhibitor risk, and that prophylaxis can turn severe hemophilia symptoms to moderate hemophilia and increase quality of life and life expectancy. While the quality-adjusted life year (QALY) cost of prophylaxis can sometimes seem very high, the preventative impacts must be clearly understood by health economists and healthcare funders.

A 2011 survey done in four European countries of young adults with severe hemophilia on prophylaxis, on-demand, or combined therapy yielded compelling findings on the benefits of early and lifelong prophylaxis. Other studies show the benefits of prophylaxis in adulthood and the impacts of prevention of a single bleed. The Swedish HTA of hemophilia therapies is now underway to assess factor product brands in terms of efficacy and reimbursement, and compare prophylaxis and on-demand regimes. "It is imperative for HTA bodies to look at the role of prophylaxis in the prevention of inhibitors, joint damage, joint surgery, immobility, and loss of employment, the costs saved in later life if these complications are prevented, and the impacts of prophylaxis on quality of life," Mr. O'Mahony said.

HTAs mainly involve systematic evaluation of the properties, effects, and/or impacts of health technologies, said Albert Farrugia, VP Global Access of the Plasma Protein Therapeutics Association (PPTA). The main purpose is to inform healthcare policymaking and funding allocations. Most HTAs tend to focus on cost-effectiveness analysis, which calculates cost, in terms of dollars, relative to a health benefit (e.g., number of bleeds avoided); and cost-utility analysis, which calculates costs relative to the quality-adjusted life year. The QALY is a way to quantify the health technology cost and benefits relative to perfect health. However, some features of cost-utility analysis are problematic for hemophilia: "The long-term benefits of prophylaxis such as less joint damage in later years and fewer surgical interventions, are discounted and this has an enormous effect on the cost per QALY," he said.

The Plasma Protein Therapeutics Association is working on a new cost-utility analysis for severe hemophilia. The model compares prophylaxis to on-demand treatment and looks at transitions between different health states over time. The model assesses joint bleeds as well as co-morbidities that affect soft tissues such as intracranial, gastrointestinal and renal bleeds, inhibitor incidence, and other factors. It also inputs randomized controlled trials that show that prophylaxis decreases incidence of inhibitors, which has a significant effect on cost of lifelong treatment. The analysis is still underway.

Dr. Sanford Schwartz of the University of Pennsylvania School of Medicine (USA) spoke about comparative effectiveness research and the opportunities to strengthen the evidence base to better inform policy and practice, and advance the field of hemophilia. Traditionally, decisions for the management of hemophilia and other medical conditions have been based on safety and efficacy. Comparative effectiveness, also called relative effectiveness, looks at how well a therapy works compared to alternatives. The goal is to guide evidence-based decision-making. Beyond randomized clinical trials, evidence from registries, observational data, and patient-reported outcomes play an important role in focusing on the patient needs. In hemophilia, it means assessing not only costs per bleed but also productivity and quality of life. With prophylaxis, more focus is needed on functional status, intracranial, gastrointestinal and kidney bleeds, and the benefits and savings. These aspects have not been sufficiently addressed in previous studies. Medical interventions must be assessed using novel analytical approaches. Good medical assessments will require a broad range of empirical data including observation, synthesis, modelling, and patient-reported outcomes and preferences.

Update on Inhibitors

Inhibitors are currently a top-ranking safety issue in hemophilia treatment. In the audience poll at the start of this Global Forum, 54% of participants selected inhibitors as the biggest safety threat today. The presentations provided the latest information from studies related to inhibitors. Dr. Carol Kasper of the Los Angeles Orthopaedic Hospital (USA) described the context for the development of the Bethesda assay and the trade-off in terms of sensitivity and specificity of the test with the assignment of any cut-off value for determining the presence of an inhibitor. The Bethesda test was developed in 1975 by a committee of hematologists. The aim was a uniform inhibitor test for the United States; prior to this, laboratories each had their own inhibitor testing method, using different conditions and different definitions of a unit. The parameters of the Bethesda test were derived through compromise; therefore the test was not the most sensitive possible. When the Bethesda paper was first published, an accompanying letter discussed modifications to increase sensitivity to measure very low level inhibitors.

Today, inhibitors data is collected to survey the hemophilia population and inhibitor patients, investigate possible correlations, or exclude certain patients from studies or clinical trials. Much discussion surrounds the correct cut-off point; in fact, the cut-off point is an arbitrary decision. A high cut-off point reduces false positives and a low cut-off point reduces false negatives. In some cases a different cut-off point might be used such as in the absence of a reference laboratory to perform the test, wherein the local criteria for an inhibitor would need to be used.

Dr. Elena Santagostino of the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center (Italy) gave an update on two initiatives. The Study on Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) is a randomized clinical trial investigating the role of product type in risk of inhibitor development in patients with severe hemophilia A. Possible limitations of SIPPET are that it considers product brands as belonging to one of two classes (recombinant or plasma-derived FVIII/VWF); and it also includes patients minimally exposed to blood components, who are known to have different risk factors and pathogenesis of inhibitors than previously untreated patients. Among its strengths, SIPPET compares recombinant and plasma-derived products in the frame of current clinical practice. There are currently 23 countries involved from around the world. The global recruitment platform means that the results will be applicable to all patients with severe hemophilia A worldwide.

The European Haemophilia Safety Surveillance System (EUHASS) monitors a range of adverse events in patients with hemophilia, von Willebrand disease (VWD), and rare bleeding disorders including inhibitor occurrence, transfusion-transmitted diseases, infections, allergic reactions, thrombosis, malignancies, and deaths. There are 23,811 hemophilia A and B patients registered from 64 treatment centres in 27 European countries. To date, no differences have been found between concentrates. EUHASS is now taking steps to prepare for monitoring new products with prolonged half-life.

Mike Soucie of the U.S. Centers for Disease Control and Prevention (CDC) described their work towards the development of a national surveillance system for inhibitors. The U.S. Hemophilia Inhibitor Research Study started out as a pilot study on the feasibility for national inhibitor surveillance according to the European Medicines Agency (EMA) guidelines published in 2006, which called for centralized or very strictly quality-controlled inhibitor testing, centralized genotyping, and prospective collection of product exposure data. The study initially focused on collecting data on treatment exposure, complete gene sequencing, and inhibitor testing. The current focus is to augment the product exposure database, advance the mutations database maintained by the CDC Hemophilia A Mutation Project (CHAMP), and gather more U.S. mutations data as well as population-based mutation and inhibitor data from defined geographic regions worldwide to examine differences in mutations and inhibitor rates.

There are currently 17 treatment centres involved, with more than 1,000 patients enrolled. Nearly 3,000 inhibitor tests have been performed; testing is done annually, prior to a planned product switch, or in the presence of clinical indications of inhibitors. The study has led to recommendations for routine monitoring of all hemophilia patients for inhibitors in a centralized laboratory, case surveillance for incident cases, and retrospective investigation of new inhibitor cases. Surveillance will be especially important for the new products coming on the market.

Inhibitors are a very serious complication in mild and moderate hemophilia as it is possible for the inhibiting antibodies to not only render the infused factor concentrates ineffective but also neutralize the endogenous factor, said Dr Corien Eckhardt of the Academic Medical Center (Netherlands). She described two ongoing studies of inhibitors in mild and moderate hemophilia. The Insight Study is investigating the association between F8 genotype and inhibitors. Clinical data was collected on 2,700 mild and moderate hemophilia A patients treated between 1980 and 2010 at 34 treatment centres across 11 countries. More than 95% of the inhibitor patients had a mutation in two specific regions, the light chain of the *F8* gene and a small region of the A2 domain. These patients had a fivefold increased inhibitor risk compared to other patients.

The Treatment of Inhibitors in Mild/Moderate Hemophilia (TRIM) Study found that 74% of the patients who developed inhibitors needed treatment for bleeding or surgery during their inhibitor episode. Inhibitor eradication therapy was initiated in 28% of the patients and was successful in about 68% of these patients. The data will be analysed further for insight into the best approaches to inhibitor treatment and eradication.

Clinical Trial Design

In recent years, clinical trial design has emerged as an important issue in hemophilia in terms of new products for market authorization. This session addressed some of the challenges of clinical trial design in hemophilia, and the progress of the International Society of Thrombosis and Haemostasis (ISTH) FVIII/FIX Scientific Subcommittee project groups on clinical trial design and harmonization of regulatory requirements for potency labelling.

Dr. Jerry Powell, Director of the Hemostasis and Thrombosis Center, University of California Davis (USA), noted that hemophilia treatment is on the cusp of a major milestone as long-acting products move towards market approval. New products now in clinical development include same factor molecules produced by new manufacturing processes, altered factor molecules with extended half-life, and biosimilars. Long-acting factors are shifting the treatment paradigms but the correlation between factor level and phenotype remains. When there is minimal molecular change, there is theoretically no reason to anticipate problems, he said.

He proposed several ways to improve clinical trial design given the current context. First, enlarge the pool of hemophilia A patients who can participate in clinical trials by making the eligibility criterion less than 2% factor level because the current practice of less than 1% factor level renders 30 to 40 percent of patients ineligible. Second, clinical trials should focus only on factor level and patient assessment of product efficacy; and monitor inhibitor formation for 20 exposure days (twice the mean exposure days of inhibitor occurrence in previously treated patients), rather than 50 exposure days. Finally, for novel long-acting products, assess number of days of factor level above 10% since the exposure day might not be the same day of infusion.

Dr. Donna DiMichele, Chair of the ISTH FVIII/FIX Scientific Subcommittee Clinical Trial Design Project Group, noted that multiple products are currently entering into pre-registration clinical trials but the availability of hemophilia patients for clinical trials is limited due to regulatory enrolment requirements. Moreover, regulatory agencies have different requirements for pre- and post-registration safety and efficacy assessment of factor concentrates.

The project group's mandate is to refine clinical outcome endpoint definitions (clinical severity, prophylaxis, inhibitors, bleed event, and response to treatment), and optimize clinical trial design requirements (numbers and types of subjects for safety/efficacy trials and surgery trials, study duration, exposure requirements, and assay methodology). The project group is examining alternative clinical trial design and statistical modelling for five types of clinical trials: FVIII biosimilars and novel biologics, FIX biosimilars and novel biologics, and novel FVIII and FIX bypassing agents.

A subgroup has formed to re-examine immunogenicity clinical trial requirements for FVIII/FIX biosimilars using currently known neoantigenicity data. In parallel, a subgroup on clinical endpoints and patient-reported outcome measures will liaise with stakeholders on consensus definitions for relevant, objective clinical efficacy endpoints and patient–reported outcome measures. The project group will submit a final report to the ISTH FVIII/FIX Scientific Subcommittee in 2013.

Dr. Alok Srivastava, WFH VP Communications and Public Policy, gave an overview of the ISTH Project Group on Potency Assignment of FVIII and FIX Concentrates, chaired by Dr. Anthony Hubbard. Several issues within current practice need to be addressed. Most service laboratories use clotting assays based on activated partial thromboplastin time (APTT) to assess recovery after infusion and it can be difficult to correlate with products labelled by chromogenic method. Assay discrepancy issues with specific products are often inadequately addressed. Designing assays for modified factor products with novel structures or functions is a challenge. Differences in regulatory approaches also need to be reconciled.

The project group has drafted recommendations on manufacturer responsibilities for potency labelling of biosimilars and novel products. New products should be tested against the World Health Organization (WHO) International Standards for FVIII and FIX Concentrates. FVIII assays should be performed using both one-stage clotting and chromogenic methods following the ISTH recommendations, and assess potency against an appropriate factor concentrate reference and a plasma reference standard.

The project group has also drafted recommendations on pharmacokinetic studies. They should be performed according to current guidelines; longer sample interval times may be required for long-acting products. *In vivo* recovery should be based on potency and post-infusion assays against the product standard. The predicted recovery for specific assay systems should be described in the registration dossier and package insert; this information may also need to relate to specific one-stage assay reagents in use in different parts of the world.

Novel Technologies

The hemophilia community is on the verge of a new generation of therapies that represent the first truly significant change in hemophilia treatment in about 20 years, said David Page, chair of the WFH Blood Product Safety, Supply and Availability Committee. This session focused on an ongoing gene transfer study in hemophilia B now in clinical trial, the development of solvent detergent technology for viral inactivation of cryoprecipitate, and other novel therapies and technologies currently in the pipeline.

Dr. Amit Nathwani of the UCL Centre for Stem Cells and Regenerative Medicine (U.K.) described the ongoing Haemophilia B Gene Transfer Study. The gene therapy is based on the adeno-associated viral vector (AAV), which is well suited for gene transfer due to its strong safety profile, endemic prevalence, and replication only by co-infection with a helper virus such as an adenovirus. The investigators engineered "self-complementary vectors" (scAAV) to allow mediation of higher levels of expression using lower amounts of vector particles.

Pre-clinical trials assessed gene transfer via peripheral vein delivery compared to hepatic delivery; the same vector biodistribution, gene transfer and FIX expression levels were achieved. The clinical trial aims to assess the safety of a simple bolus infusion of the scAAV at three dose levels administered into the peripheral vein, and determine the dose required to achieve stable FIX expression above 3% of normal. Six subjects to date have received the novel vector. Peripheral vein infusion was very well tolerated. There is evidence of stable FIX expression at 1-12% of normal in all six subjects for between 5-16 months; four have been able to stop prophylaxis and two have been able to extend the interval between prophylaxis. The savings on prophylaxis for the U.K. government so far is of the order of £300,000. The study, which initially recruited patients from the U.K. only, is now open to patients worldwide.

Dr. Magdy El Ekiaby of the Cairo Shabrawishi Hospital Blood Transfusion Centers (Egypt) described new solvent detergent cryoprecipitate technology which offers safer treatment for patients who rely on fresh blood components. The single-use solvent detergent pathogen inactivation medical device will enable blood centres to process mini-pools of plasma components. The technology is simple and requires no additions to the blood services.

Validation studies have been run in Cairo, Paris, and Lille. The viral validation study conducted in Paris found that the virus inactivation technology is very fast and effective. The device is now being tested and validated at other blood centres. Results from the Thai Red Cross were almost identical to the Cairo results; other validation sites include Saudi Arabia and Tunisia. A small pharmacokinetic study was conducted in severe hemophilia A patients without inhibitors. No adverse events were observed. FVIII half-life was about 14 hours and the clearance rate was similar to plasma-derived and recombinant FVIII concentrates. Patients reported 8 to 22 days free from bleeding episodes after infusion; compared to their previous pattern of one bleed every 7 to 10 days. The solvent detergent cryoprecipitate has been used in a number of surgical procedures. Successful hemostasis was achieved in all procedures with neither bleeding episodes nor any adverse events.

Finally, there were a number of presentations from the pharmaceutical industry on promising products in the pipeline for both more potent and longer-acting factors, some of which are now in clinical trial phases and could possibly be on the market in two to three years.

Dr. Debra Bensen-Kennedy of Clinical Research and Development at CSL Behring, described current research and development activities to advance treatment for rare bleeding disorders. CSL Behring is focusing on half-life extension of recombinant activated factor VII (rFVIIa) and recombinant factor IX (rFIX). The research has focused on albumin fusion technology, on the hypothesis that fusion of recombinant factor and recombinant albumin could extend the factor half-life through the extended half-life of albumin. CSL Behring is also engineering an improved factor VIII. Researchers have created a single chain DNA construct with an increased heavy/light chain association and enhanced molecular integrity with faster, more efficient binding to VWF. Comparable efficacy was shown in tail tip bleeding models. The formal development phase is underway. CSL Behring has also developed a highly active plasma derived FVIII/VWF concentrate for the treatment of hemophilia A and von Willebrand disease. The product Biostate® was launched in Australia in 2003 for hemophilia A treatment and has been registered for VWD treatment in Australia and New Zealand since 2008. It is currently in clinical trials moving towards centralized approval in the European Union.

Dr. Prasad Mathew of Bayer described some novel longer-acting treatment options being developed to address significant unmet medical needs in hemophilia care. Bayer is developing a novel longer-acting FVIII compound, BAY 94-9027, which contains a single B-domain deleted site-specific pegylation. Compared to recombinant factor FVIII (rFVIII), the novel FVIII compound had a two- to threefold increase in half-life in animal models, prolonged efficacy in bleeding models, and reduced immunogenicity in pre-clinical tests. There was also an 80% reduced uptake in human dendritic cells, reduced activation of FVIII-specific T cells, and significantly reduced FVIII-specific antibody formation. Bayer has now initiated a Phase I trial to assess pharmacokinetics and safety following single and multiple dose administration.

Another product in development is BAY 86-6150, a novel rFVIIa compound that contains six amino acid changes resulting in increased binding to activated platelets, increased thrombin generation, reduced activity with tissue factor, increased half-life, and increased and prolonged efficacy in animal models. A Phase I study has confirmed improved pharmacokinetics. Phase II/III trials will start in 2012. The products in the Bayer pipeline have the potential to increase convenience and thus support patient compliance, he said. The extended FVIII half-life and efficacy of BAY 94-9027 would help optimize prophylaxis therapy and preserve on-demand efficacy, while the novel rFVIIa product BAY 86-6150 would enable effective bypass therapy. Other novel clotting factors and bypass compounds are also being researched and evaluated.

Dr. Snejana Krassova described Biogen Idec's efforts to harness the neonatal Fc receptor (FcRn) recycling pathway to fuse and transport rFVIII and rFIX proteins, using proprietary monomer technology. Pre-clinical trials of rFVIII-Fc showed a twofold increase in half-life compared to rFVIII while rFIX-Fc pre-clinical trials showed a three- to fourfold increase in half-life compared to rFIX. Both rFVIII-Fc and rFIX-Fc had acute activity and dose response comparable to their market counterparts, as well as prolonged pharmacokinetic and prophylactic properties.

Phase I/IIa studies of rFVIII-Fc at two dose levels in patients with severe hemophilia A and of rFIX-Fc at six dose levels in patients with severe hemophilia B showed increased half-life, comparable incremental recovery, and no adverse events. The A-LONG Phase III Pivotal Study of rFVIII-Fc and B-LONG Phase III Pivotal Study of rFIX-Fc aim to assess safety, tolerability, and efficacy; and characterize the pharmacokinetic profile and range of doses and schedules required to adequately treat bleeding episodes on-demand, prevent bleeding in a prophylaxis regimen, and maintain hemostasis in a surgical setting. Both fusion protein products hold promise to improve the lives of people with hemophilia by reducing the frequency of infusions while enhancing efficacy, she said.

Kim Jacobsen of Novo Nordisk gave an overview of factor XIII deficiency and their development of the first recombinant product for treatment of FXIII deficiency (rFXIII), the manufacturing process, and the product's safety and efficacy. The normal circulating concentration of rFXIII is 50% to 150%, with a half-life of about 12 days. The Phase III clinical study was designed for monthly dosing and trough level above 10% after four weeks. There were 23 participating centres from 11 countries in Europe, the Mediterranean, and North America. The pivotal Phase III efficacy and safety trial sought to determine the rate of bleeding episodes requiring treatment with a FXIII-containing product, over a 52-week treatment period. rFXIII outcomes were compared to a historical control rate based on retrospective data from 2005. The rFXIII study showed high efficacy in prevention and reduction of bleeds. There were no severe bleeds and no intracranial or life-threatening bleeds; all the bleeds were trauma-related. The trial demonstrated that rFXIII provides a safe treatment option for patients with FXIII A-subunit deficiency. rFXIII appears to be a safe and efficacious treatment for people with congenital FXIII deficiencies and has been submitted to both the U.S. Food and Drug Administration and the European Medicines Agency for approval.

Conclusion

The 2011 Global Forum presented many perspectives on important topics in the treatment of hemophilia and other rare bleeding disorders. The sessions were both informative and thought-provoking, and generated constructive dialogue and debate. Despite the progress and advances in treatment, there are still tremendous unmet needs around the world. There was broad agreement on the importance for all stakeholders in the bleeding disorders community to work together on the issues to find solutions to ensure global access to safe and effective treatment, and collaborate on research and initiatives to support the development of new products and avenues for treatment. The WFH will integrate the information and knowledge gained from this global forum into its programs and activities going forward.

Key Points from the Seventh WFH Global Forum

- The blood system must pay close attention to progress and developments in blood safety and supply, and respond to evolving public needs and new challenges using the best available science to support decision-making. Currently, a number of complex issues need to be balanced to address the increasing demand for blood products: blood safety, donor recruitment and screening, epidemiology, pathogen testing, risk surveillance, and risk management.
- It is important for the bleeding disorders community to engage in health technology assessments and comparative effectiveness research, and gather and provide observational and experiential outcomes data to supplement the clinical data in order to ensure that the benefits and impacts of treatment are clearly understood by health economists and healthcare funders.
- National and international surveillance systems for inhibitors provide important information on inhibitor development and incidence, which allows research and analysis of risk factors such as gene mutations, product exposures, and product switching; and investigation of the best approaches to inhibitor treatment and eradication. Surveillance will be especially important for the new products coming on the market.
- Clinical trial design and harmonization of potency labelling and regulatory requirements are important challenges that need to be addressed, particularly for novel therapies such as long-acting factors and biosimilars. Issues include restrictive clinical trial eligibility criteria, different regulatory requirements for pre- and post-registration safety and efficacy assessment of factor products, and the use of different assay methods around the world. Consensus definitions of clinical outcome and clinical efficacy endpoints are needed.

NOTES

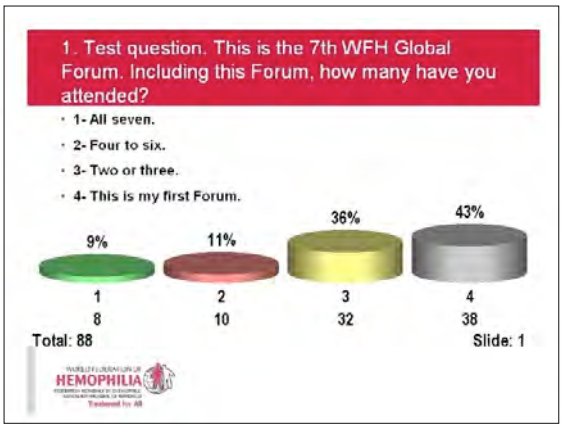
DAY 1: SEPTEMBER 22, 2011

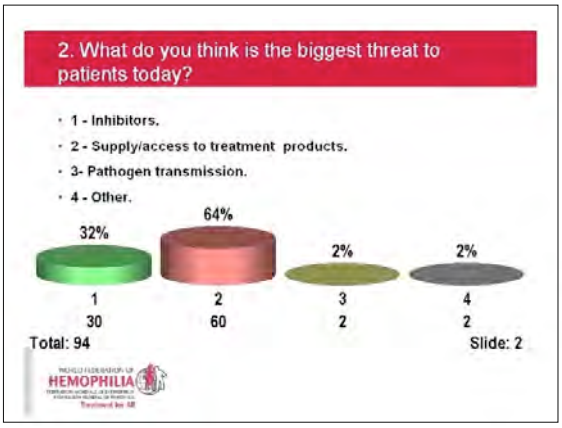
Welcome & Opening Remarks

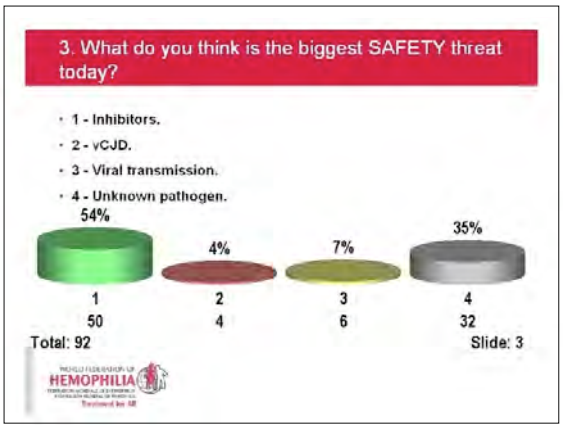
Claudia Black, CEO and Executive Director of the World Federation of Hemophilia (WFH), welcomed more than 140 international participants to the Seventh WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders. It is now over 10 years since the first WFH Global Forum in Montreal in April 2000. Held every two years, the meetings continue to generate important debates and discussion. This year's program focused on current knowledge and perspectives on blood safety risk, trends in healthcare funding and allocation of resources, inhibitors research, clinical trial design issues, harmonization of regulatory requirements for potency labelling, and novel therapies and technologies.

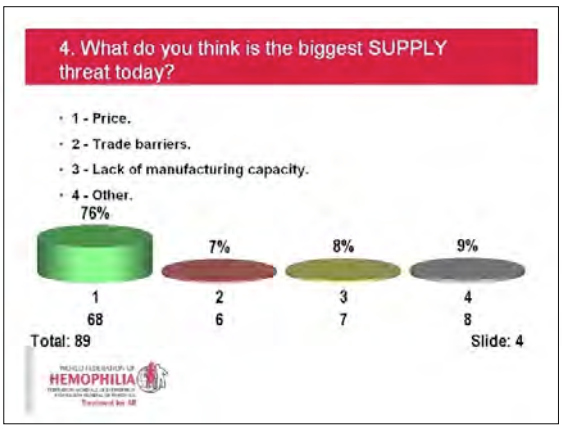
The WFH Global Forum aims to present the latest developments in treatment safety and supply and in particular to stimulate discussion and debate, said WFH President Mark W. Skinner. A key goal is to try to improve consensus and understanding around the world on the issues of the day. Participants at this meeting broadly represented the diverse stakeholders in the global bleeding disorders community: regulators, ministry of health officials, blood agency representatives, patients, clinicians, researchers, and industry partners. Throughout the forum, participants were polled to capture their viewpoints on a comprehensive range of topics and concerns.

Global Forum 2011 received vital funding and support from three official sponsors: Héma-Québec, Ministère des Relations Internationales du Québec (Québec Ministry of International Relations), and Ministère de la Santé et des Services Sociaux du Québec (Québec Ministry of Health and Social Services). Additionally, Biogen Idec contributed funds in support of WFH travel grants.









Session 1: Perspectives on Risk

CHAIR: DR. MAGDY EL EKIABY, MEDICAL EXECUTIVE, WORLD FEDERATION OF HEMOPHILIA (WFH)

The HIV/AIDS pandemic in the 1980s and 1990s tragically affected the hemophilia community and other patient populations relying on blood products and led to the concept of blood safety for both transfusion services and industry focused on blood-borne pathogens and the prevention of viral transmission through blood components, said Dr. Magdy El Ekiaby. Measures were taken to augment the stringent precautions for plasma collection for fractionation and ensure that recombinant products adhere to a high safety margin. Many countries established national systems and legislative and regulatory frameworks to ensure the safety of the plasma; today, plasma fractionation is mainly done in Western world. At the same time, the reality is that societies globally are witnessing several challenges that need to be addressed in the next decades:

- *Demographic changes:* In recent decades, the birth rate in Western Europe has fallen 30% (from 2.1% to 1.5%) and the number of inhabitants in Western Europe is expected to decline by 70 to 80 million in the next few decades, which will have an impact on the size of blood donor populations.
- *Intensifying global mobility:* More Europeans are travelling to endemic areas where malaria and other diseases are prevalent and their deferral from blood donation will affect the donor base and blood supply.
- *Emerging pathogens:* New pathogens in humans (variant Creutzfeldt-Jakob disease in the U.K., West Nile virus in the U.S., etc.) also have an impact on donor deferral and the blood supply.

Dr. El Ekiaby noted that 75% of the global population resides in Asia, the Middle East, and Africa but they do not contribute to the global plasma supply because they do not meet the international blood safety criteria. They consume only 25% of the global supply of clotting factor concentrates—this means that the majority of people with hemophilia around the globe are at risk according to the western standards, he said. "Given this context there needs to be another perspective on risk because a concept based on zero risk will probably put this concept of blood safety and supply at risk."

Risk-based decision-making for blood safety

DR. JUDIE LEACH-BENNETT, EXECUTIVE DIRECTOR, RESEARCH & EDUCATION, CANADIAN BLOOD SERVICES

The issues of blood collection, blood safety, and risks to supply and availability are important concerns to a wide variety of stakeholders: blood recipients, policymakers, regulators, industry, and the general public. Dr. Judie Leach-Bennett gave an overview of the International Consensus Conference on Risk-Based Decision-Making for Blood Safety held in Toronto in October 2010, which resulted in a consensus statement on the necessary components of a risk management framework.

The failures of blood systems in the 1980s and 1990s continue to shape the current decision-making paradigm for blood safety. "But with increasingly complex systems and challenges, the paradigm has resulted in inconsistent decisions; cases of misapplication of the precautionary principle, inaction pending sound evidence, and like situations not treated in like manner," she said.

The primary pursuit of "freedom from transmissible harmful agents" has been important and very successful but also expensive and controversial, with impacts on supply. Risk interventions to prevent HIV, HCV and HBV transmission are important and provide a demonstrable improvement in safety. However, there is disagreement surrounding interventions such as the variant Creutzfeld-Jakob disease (vCJD) deferral and universal pre-storage leukoreduction.

Issues and questions pertaining to risk prevention and interventions for blood safety include:

- Is the decision-making paradigm overly biased towards transmissible risks at the expense of risk along other points in the "vein-to-vein" continuum?
- Are regulations being unduly driven by a self-protective mechanism on the part of regulators?
- Are risk reduction measures driven by industry or test manufacturers?
- Have some interventions paradoxically reduced safety?

Absent an appropriate decision-making framework, there is a zero-risk decision-making paradigm in which no intervention is too expensive. Until now, little attention has been paid to the notion of opportunity cost (i.e., looking at where the scarce healthcare dollars can be invested for a greater benefit elsewhere) but there is recognition that a zero-risk paradigm is not sustainable. This leads to the concept of acceptable risk, acceptable to whom, and acceptable under what conditions.

The International Consensus Conference on Risk-Based Decision-Making for Blood Safety convened experts from blood organizations and industry to examine the current paradigm and make recommendations for a standardized framework to guide decision-making within blood systems. There was broad participation from international blood operators including Canadian Blood Services, America's Blood Centers, American Red Cross, U.K. National Health Service Blood & Transplant, European Blood Alliance, Australian Red Cross Blood Services, Héma-Québec, and the American Association of Blood Banks. A consensus panel with expertise in risk management, bioethics, transfusion medicine, public health, and patient advocacy was formed to engage participants in discussion and draft a consensus statement for moving forward.

The consensus panel identified a need for a decision-making framework that, as much as the science and historical context of blood safety, addresses socio-political issues such as social and ethical values, economics, and public expectations. Transparency, flexibility, and the principles of proportionality, non-discrimination and consistency are essential. There is also a need to develop competencies in risk concepts (risk assessment, acceptable risk, risk communication, etc.) and a paradigm other than zero risk. Transparency and broad participation are essential to cull the perspectives on risk among the general public and particularly patients and blood recipients who bear the risks.

The conference covered a comprehensive range of topics from historical perspectives to recent experiences such as decision-making around vCJD, hemovigilance programs developed in Quebec and the U.K., and case studies involving the precautionary principle. Sessions also focused on risk management frameworks, risk assessment and modelling, regulatory perspectives, and elements and principles of decision-making. The panel identified aspects and limitations of current decision-making in blood safety: drive to minimize a risk with minimal attention to cost; focus on infectious disease transmission; precautionary principle applied in different ways across different issues; focus on product quality and convergence of standards; unsustainable zero-risk paradigm; little consideration of the notion of cost and opportunity of cost; and the economic reality of increasingly constrained healthcare spending.

The panel noted five elements that are important to any comprehensive blood safety approach:

- Integrated risk management framework that encompasses the "vein-to-vein" continuum and beyond (from blood donor recruitment through any adverse effects in recipients of blood products); and brings together all sectors of the blood system nationally and internationally in risk management decision-making at the global level.
- Decision-making based on transparent risk management principles and correct application of the precautionary principle.

- Meaningful engagement with stakeholders throughout the risk decision-making process.
- Risk management strategy within the context of well-established ethical principles to ensure that the rights of both donors and patients are respected.
- Forward-looking and proactive risk management that anticipates and prevents risks, and incorporates the proportionality principle (a missing link in the current system).

A number of best practices for risk-based decision-making were identified:

- principles and guidelines of risk management;
- framework that involves risk identification, analysis, monitoring, and communication;
- qualitative and quantitative risk assessment;
- recognition of the economic and cost constraints that impact elements of the blood system;
- integrated "public risk network" approach involving all levels of the blood system.

The framework should incorporate the key concepts that blood services are distinctly a social good accompanied by societal obligations of safe and efficient production and fair and accountable distribution; and that blood is a special type of medical resource derived from an altruistic source, which has special meaning for those who give and those who receive it.

The panel also highlighted important components to incorporate into the design of a framework: valid data on risk profiles; analysis of costs and benefits of treatment, and the costs of failing to treat; an ethical system for decision-making; and interim assessments of performance for continuous learning and improvement. "There can't be silos in coming to these decisions. Across the vein-to-vein system there must be a shared understanding of risk assessment, and shared metrics and evaluation of the risk," Dr. Leach-Bennett said. She emphasized that particular attention and consideration must be given to those individuals who have been harmed by past failures.

Finally, there needs to be commitment and integrated collaborative effort by leaders to develop a framework, methodology, and governance structures for risk-based decision-making in the blood system. The next steps will be to convene all relevant stakeholders to gather the data, set priorities and objectives, and fill the knowledge gaps.

Discussion

A participant noted that the risk-based decision-making framework is a very important aspect of looking after patients globally but the consensus conference seems to have excluded a large part of the world. Dr. Leach-Bennett said that the consensus panel recognized that this issue is relevant globally—these were initial steps and there is commitment to continue the discussion in a much broader scope.

Moving forward, it will be important to research how well the concepts of risk and sustainability are actually understood, particularly from the recipient point of view. "In general, people recognize that zero risk may not be possible. Still, they are not prepared to accept risk that can be removed from the system," a participant said. Another issue is the notion of reallocation of dollars and resources to other areas. There isn't much evidence that this would actually be done. Dr. Leach-Bennett agreed that there is insufficient research on the different perspectives on risk tolerance and acceptable risk. "The debate shows that we have to look at blood safety across the vein-to-vein continuum and beyond. From a system perspective, we need to step back from our organizational silos to discuss the priorities and make good decisions to manage the risks," she added.

The Debate on MSM Donors and Discussion of Future Research

Measures to reduce risks should not be considered permanent and immutable—when the environment and situation changes, it is important to review previous decisions, said Dr. Magdy El Ekiaby, session chair. One such review is currently taking place within several fora in regards to policies for the lifetime ban on blood donations from men who have sex with men (MSM). The first two presentations explored the appropriateness of revising this measure.

Advocacy to Revise Blood Donation Policies for MSM

NATHAN SCHAEFER, DIRECTOR OF PUBLIC POLICY, GAY MEN'S HEALTH CRISIS, NEW YORK, USA

The current position of Gay Men's Health Crisis (GMHC) is more balanced and nuanced than in the past, Nathan Schaefer stated. In the past, GMHC called for a repeal of the lifelong deferral of blood donations from men who have sex with men (MSM). Today, the agency is advocating for a revision of blood donation policies to end the perception of discrimination against gay men while also increasing the safety and supply of blood donations.

Gay Men's Health Crisis provides services to 12,000 clients each year. The agency understands the impact of blood safety on people with bleeding disorders and is committed to maintaining the safety of the blood supply. At the same time, GMHC appreciates the importance of people donating blood. While gay men are significantly more likely to be HIV-positive than other men (44 times more, according to one study), most gay men are not HIV-positive and not all gay men are at equal risk. GMHC is not advocating for all gay men to donate blood, but for changes to the deferral policy that reflect actual levels of risk and acknowledge the importance of increasing blood supply.

There are significant negative consequences to the current lifelong MSM deferral policy:

- It leads to perceived discrimination that results in a significant loss of potential blood donors, not just among gay men but also from those participating in protests and boycotts, particularly college students who would otherwise participate in campus blood drives.
- It perpetuates the notion that all gay men are equally at risk.
- It promotes the false perception of low HIV risk among young heterosexuals, who think that if they donate blood, they do not need to be tested for HIV.
- It is a missed opportunity to promote public health and safer sex practices through more rigorous exclusion criteria that asks all prospective donors about high-risk behaviours.

There is evidence that not all gay men are at high risk for HIV; according to several sources, gay men are twice as likely to use condoms during sex as their heterosexual counterparts. Focusing the deferral on a target group rather than high-risk activities creates significant inconsistencies and is not optimally effective in protecting blood supply, Mr. Schaefer said. "It's not being a gay man or even having sex with another man that puts you at risk for being HIV-positive. It is having unprotected sex, particularly unprotected anal sex."

Support for policy reform has been increasing recently. Among those advocating changes to the deferral policy are several prominent politicians including U.S. Senator John Kerry and several other senators and members of the House of Representatives. Significant support has also come from blood services including the American Association of Blood Banks, American Red Cross, and America's Blood Centres. A joint statement was also issued by several prominent lesbian, gay, bisexual, and transgender (LGBT) groups and hemophilia groups, emphasizing their commitment to the safety of the blood supply and support for a review of current policies.

The collaboration between the communities is notable and important as HIV has disproportionately affected gay men and people with hemophilia, and both would benefit from policy change, he said. "Working together has made our advocacy position stronger. The lessons learned are much bigger than revised policies for gay men and extend to a broad agenda for blood donation reform." GMHC promotes alternative approaches that increase public awareness while not deterring people from blood donations—it does not support boycotts or protests, particularly on college campuses.

A June 2011 recommendation by the U.S. Advisory Committee on Blood Safety and Availability (ACBSA) acknowledged that current blood donor deferral policies are suboptimal, permitting high-risk donations while preventing some low-risk donations, but currently available scientific data are inadequate to support change to a specific alternative policy. Therefore, until further evaluation, the committee recommended that the current indefinite deferral for men who have had sex with another man even once since 1977 not be changed at the present time.

In July 2011, the U.S. Department of Health and Human Services released a document on its progress since the ACBSA recommendations. The Blood, Organ, Tissue and Safety work group has been charged to devise a workplan to review the policy, and additional studies will be done to determine whether potential blood donors correctly understand and properly interpret the current standard questionnaire used to obtain donor history and whether MSM would be likely to comply with revised deferral criteria.

A key question is whether an alternative screening strategy (e.g., pre- and/or post-qualifying donation infectious disease testing) for MSM (and potentially other high-risk donors) would assure blood safety while enabling collection of data that could demonstrate safe blood collection from a subset of MSM or other currently deferred donors (e.g., men with a history of abstinence from MSM behaviour for a defined time period). "It's been widely acknowledged that, prior to HIV, gay men were reliable donors. Understanding donation behaviour is what will make people more prepared to make better decisions about blood donation policies," he concluded.

MSM Donor Deferral

MARK W. SKINNER, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA (WFH)

The gay and blood recipient communities have both been disproportionately impacted by the HIV epidemic and have a history of working together to provide HIV support, research advocacy, treatment access, and prevention programs. "We have a shared history and a shared commitment to blood safety. Don't assume we're at opposite ends of a perspective," said WFH President Mark Skinner. His presentation focused on blood donor deferrals and recent efforts to revisit the lifetime exclusion of men who have sex with men (MSM) from donating blood.

The precautionary principle has two components. It requires that measures be put in place to minimize risk, and that the measures be reviewed as knowledge increases or changes. It is important to ask whether the lifelong blood donation deferral for MSM is still appropriate and whether there is enough scientific information available to make a change. While value judgments do factor into these decisions, it is critical that they be guided by science, he said.

There have been significant social, cultural, and legal changes in the years since MSM deferral policies were originally put in place. Laws and attitudes toward discrimination based on sexual behaviour have changed and there have been significant improvements to technology, such as the reduction of the window period through NAT testing (i.e., testing of source plasma).

It is important to properly frame the debate on whether or not to change the donation deferral policy for MSM, Mr. Skinner said. This requires balancing a number of complex issues in the context of a likely increase in demand for blood products: discrimination, supply, definitions of low and acceptable risk, epidemiology, the evolution of new pathogens, and advances in knowledge and technology. There is no doubt that the MSM deferral policy is discriminatory—but if discrimination is in the interest of public health, it may be justifiable. Moreover, epidemiology in and of itself is a science of discrimination. Criteria for donor deferrals must put patient safety first and be based on large-scale epidemiological evidence. These decisions are not judgments about individual donors but measures to reduce the risks from both known and unknown pathogens.

A change in the length of the deferral period will not eliminate discrimination, it only narrows the scope and might make it more palatable, Mr. Skinner said. Only a behavioural-based system focusing on high-risk sexual behaviour, regardless of sexual orientation, will fully eliminate the discrimination issue. The important questions are whether the risk level is high enough to justify treating a segment of the population differently, and the likely impact on the blood supply.

Some of the important questions that must be answered scientifically include whether it is possible to differentiate risk based on an individual's sexual behaviours, whether number of sexual partners matters, and whether it is possible to differentiate risks by type of sexual behaviour. Spain and Italy have opted for deferrals based on number of sexual partners. Spain has a 6-month deferral for anyone who has had a change of sexual partners, while Italy has a 12-month deferral for anyone who has had more than one partner in the past year. However, asking more detailed questions on sexual behaviour could also have an impact on potential blood donors. "If a mid-western soccer mom has to answer questions about her sexual practices when she gives blood, is that going to discourage her?" he asked.

It is not possible for any medical treatment to pose zero risk, but there is a clear legal requirement that steps be taken to make them as safe as possible. Testing and pathogen reduction technologies have advanced but are not perfect. Therefore, careful donor selection remains the cornerstone of a safe blood supply system. Data from the U.S. Centers for Disease Control and Prevention (CDC) indicates that men who have sex with other men are at a higher risk for transmitting HIV or other infectious diseases than individuals in other risk categories These challenges necessitate a national hemovigilance system to report transfusion-transmitted infections; however, such systems are only as strong as the physicians doing the reporting and tracing.

In addition to HIV, HCV and HBV, there are a host of emerging pathogens which threaten the blood supply; these include previously unidentified infectious viruses that can be transmitted by blood transfusion, sexual intercourse, saliva, and/or natally (at birth). Of particular concern are infectious agents such as HTLV-1 and HHV8 which can be asymptomatic for a long time but still transmissible, as is the case for HIV. Quarantine release errors also pose a safety risk. A 2009 study by the U.S. Food and Drug Administration on the risks and benefits of possible alternative deferral strategies for MSM estimated a very small but still significant risk of a failure in blood testing, i.e., a false-negative result leading to a contaminated component being released. It is essential to determine how to minimize this risk of error, he emphasized.

As end users of blood products, it is critical to promote the importance of a strong hemovigilance and biovigilance system. A robust and systemic approach must be developed to track and counter known and emerging threats to the blood supply. Donor screening, deferral and testing measures alone are inadequate to solve such complex problems. The issue of compliance poses an equally significant risk. Recruitment messages must be conveyed clearly. Data suggests that length of deferral period may be less important than understanding of the policy and compliance with the rules. MSM and bleeding disorder communities need to work together to ensure that blood donors understand the system.

Changes to the U.S. deferral policy for MSM donors would likely have a significant impact on the international supply of blood products since 60% of the world's plasma comes from the United States, and particularly in countries that prohibit MSM blood donations.

The U.S. Department of Health and Human Services' research plan focuses on these critical questions:

- How does the risk of blood transmissible diseases in the current donor population relate to risk factors in donors?
- What is the root cause of quarantine release errors and what mitigations can be considered?
- Do potential blood donors correctly understand and properly interpret the current standard questionnaire used to obtain donor history?
- What motivates a man with MSM behavioural history to donate blood and would MSM be likely to comply with modified criteria?
- Would alternative screening strategies for MSM assure blood safety while enabling the collection of data that could demonstrate safe blood collection from a subset of MSM or other currently deferred donors?

The hemophilia community hopes that once all this data has been gathered, any decision changes to blood donor deferral can be made from a scientific perspective, not a political one, he said.

Efficacy of Testing Scenarios

DR. STEVEN KLEINMAN, BLOOD SYSTEMS RESEARCH INSTITUTE, SAN FRANCISCO, CALIFORNIA, USA

Dr. Steven Kleinman presented an overview of an international multicentre study on efficacy of testing and HIV, HCV and HBV blood screening scenarios for fractionated plasma products, focusing on data collected from the whole blood sector (i.e., from whole blood donors and not plasma donors), mathematical modelling, and general principles of efficacy and testing scenarios. The study is being run primarily out of the Blood Systems Research Institute. The objectives were:

- Classify HIV, HCV and HBV infections into various phases of infection and analyse them by geographic region.
- Compare the efficacy of different nucleic acid testing (NAT) and serology screening scenarios in first-time, lapsed, and repeat donors; calculate modelled residual risk in each region; and calculate efficacy as the percentage of transmission risk that is removed by a given testing strategy.
- Compare the cost effectiveness of these scenarios.

To ensure a standard data set, only centres using Novartis/GenProbe individual donor (ID) NAT were included in the study; the participating centres were from South Africa, the Mediterranean, Central and Northern Europe, Southeast Asia, the Pacific, and Egypt. These centres constitute a large majority of all countries that perform ID NAT. It is necessary to know the sensitivity of the assays used, the level of viral infectivity at each level of infection, and local epidemiological data. By analysing this data, it is possible to determine transmission risk, efficacy measured in percentage of risk avoided, and cost effectiveness in terms of screening costs for infections prevented.

In reviewing the natural history of early HIV infection, Dr. Kleinman noted that it is only possible to detect HIV by NAT testing after the first 10 to 15 days after transmission. HIV RNA rises quickly during this period, then antibody presence increases, which causes RNA to diminish as the antibody takes effect. In some cases, the viral titer may disappear completely and only the antibody will be detectable. By the time p24 antigen levels are detectable, viral titers are very high. Serologically detectable antibodies take even longer to reach detectable levels.

Data collected from study participants was classified by donor status (first time, repeat, or lapsed for more than one year) and included NAT or serology testing only or combined NAT and serology data. More detailed data was collected upon pathogen detection including pre-seroconversion or pre-NAT conversion intervals between donations, confirmatory NAT and serology, and follow-up test data when available to avoid false positives. Standardized definitions for phases of infection were applied by onsite investigators and reviewed by central investigators. In total over 1.5 million donations from first-time donors were examined and categorized by region.

The highest prevalence of HIV was in South Africa, which recently expanded its donor recruitment base; there were 53 NAT-detected window period (WP) infections, representing a WP NAT yield rate of 111 per million. In the other regions, the WP NAT yield rate was much lower, only about 1 per million; in fact, there was only one other WP NAT detection in all other regions combined. HIV prevalence was 10,381 per million in South Africa, compared to an average of 171 per million in other regions. In all three donor types, prevalence in first-time donations is much higher than in lapsed donations, which is in turn is much higher than in repeat donations, and WP NAT yield rates roughly parallel prevalence.

By doing NAT and antibody testing, it is possible to remove almost all risk of infectivity from the blood supply, Dr. Kleinman said. Because the empirical data is so small in these cases, it is not easily detectable. However, it is possible to mathematically model the scenario to determine residual risk for lapsed and repeat donors; risk cannot be modelled for first-time donors because the modelling requires data on interdonation intervals. The model takes into account that if NAT fails to detect the virus, the amount present must be small and have a lower level of infectivity. The data indicate that HIV residual risk is roughly equivalent for lapsed and repeat donors. Previous data suggests that mini-pool NAT yield rates in the U.S. were higher in first-time donors than in repeat donors. The investigators used the international HIV data set to model the relative risk in first-time, repeat, and lapsed donors. In South Africa, the residual risk for first-time donors was four times higher than for lapsed and repeat donors while in other regions, the residual risk for first-time donors is lower. This is likely due to recent changes to South Africa's donor recruitment policies; previously, blood donations were sought from the white population but recruitment now includes the black population, which has a much higher incidence of HIV.

Dr. Kleinman also reviewed findings on the efficacy of HIV screening assays. To date, analysis and results have only been completed in South Africa but the study is progressing in the other countries. The overall conclusion is that performing ID NAT and antibody testing (the most sensitive strategy possible) picks up 97.6% of calculated residual risk in repeat donors; performing mini-pool NAT testing instead with a pool size of 8 increases risk with 95.6% detection of the risk, while mini-pool NAT testing with a pool size of 16 detects 94.9% of the risk. Antibody testing, in conjunction with p24 HIV antigen testing picks up only 90.6% of HIV antigens and antibodies, while antibody testing alone takes away 86.4% of risk. "This is a way to quantitate what your strategies are achieving in terms of risk detection and interdiction—then the question becomes whether you are willing to pay for the individual donation NAT strategy, which is more costly," Dr. Kleinman said. The U.S. and Canada continue to do mini-pool testing because the cost of ID NAT would be considerable while the number of cases prevented is estimated to be in the range of about 1 in 5 million units. Changing from mini-pool to ID NAT testing in the U.S. would increase testing volume by up to fifteenfold to interdict two or three infections a year.

While the presentation focused on the theoretical and mathematical modelling and analysis for red blood cells, the analysis for plasma is currently being completed and will be followed by similar analyses for HCV and HBV. With transfusion of a whole unit of plasma, even lower levels of virus in the plasma, i.e., very low concentration of virus, could cause infectivity.

Discussion

A participant noted that the results so far show that in some regions outside South Africa, repeat donors have a higher infectious risk. The different risk factors in these Mediterranean groups compared to South African donors need to be analyzed. Dr. Kleinman said this finding generated a lot of discussion when it was presented at the International Plasma Fractionation Association (IPFA) meeting and the International Society of Blood Transfusion (ISBT) meeting earlier this year. One anecdotal hypothesis is that Spain and Italy, which comprise the participating countries from the Mediterranean region, do not have MSM deferral and it appears that some use the blood collection services to get their blood tested. "The epidemiology is very different in different areas and has to be done locally, but it does point to questions that local investigators can begin to ask," he said.

A participant noted that there is a spectrum of different approaches, underpinned by differences in policy. South Africa's policy change to eliminate discrimination by replacing donor selection based on race with an enhanced testing policy (i.e., ID NAT) was expensive. Is it conceptually sound and possible to substitute a measure for optimum safety with another measure, i.e., to implement enhanced testing in place of some of the current screening approaches in order to relax deferral of MSM or other deferred groups? "The concept of changing questions while enhancing pathogen testing and interdiction sounds nice, but operationally you cannot make the process extremely complex—collect a blood sample, test the sample, have individuals return to give blood—and expect to retain the same donor population," Dr. Kleinman said. "That works in Europe but probably would not work very well in the U.S. given the difference in people's behaviours."

Questions and deferral criteria can be changed in concert as part of a science-based process but he said in his view, trying to balance the risks with additional testing onsite or quarantine is impractical and will not work. "There are trade-offs. If we had pathogen reduction for all components of whole blood, I would agree we could relax deferral criteria significantly because we're putting the money in a different direction—but there won't be pathogen inactivation for red blood cells for quite a while, so we're faced with the question of whether we change deferral criteria now and whether we could enhance testing if we did so."

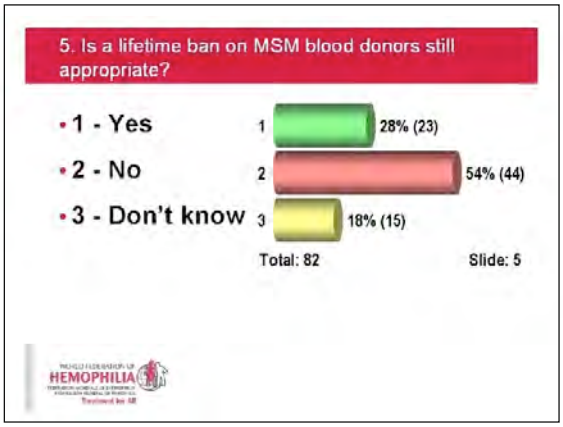
Additionally, the risks from window period units are quite small; a 12-month deferral criteria for an HIV risk factor covers well beyond the window period for a positive NAT test and testing positive for HIV antibodies. "The only risk in taking this higher risk population under this double testing scenario is quarantine release errors, which happen quite seldom with laboratory positive units," Dr. Kleinman said. "It's not zero risk—it's correct to be concerned about it—but it's not as big a player as made out to be." His personal view is that donor deferral criteria could be changed now without needing additional information to do so, given the large-scale risk analysis from the U.K. which prompted changes to the MSM deferral criteria there. The issue is being looked at in the U.S. and Canada.

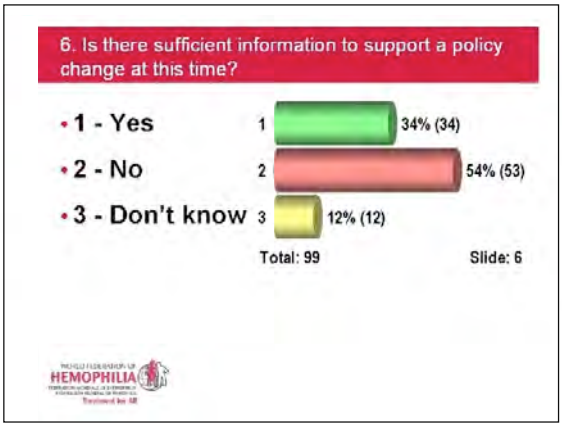
One of the subtleties in the position put forward by patient groups and the GMHC is that the patient communities are unwilling to accept an increase of risk without good understanding of that increased risk, said Mark Skinner. There also was discussion on whether there could be a rebalancing of risks to eliminate discrimination by relaxing MSM deferral, but at the same time enhance behaviour-based donor screening and deferral, such that the overall level of risk remains the same or lower. "We want a better understanding of what the different risks and trade-offs are. Perhaps this is an opportunity to include the overall risk and not just address a discrete component of it relative to MSM," he said.

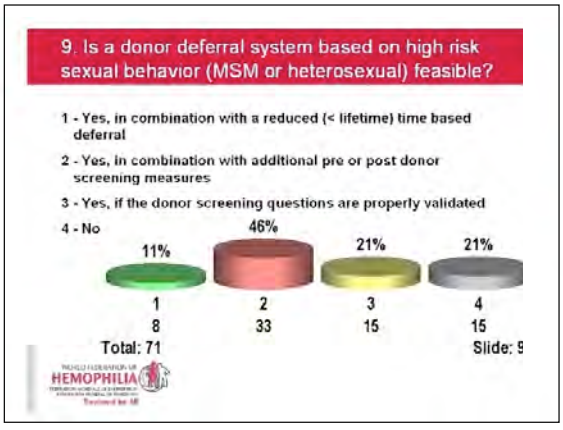
Dr. El Ekiaby noted that the decision to implement ID NAT in South Africa was made in response the public demand to eliminate race discrimination in the blood donor criteria as much as to lower transmission risk in South Africa. "The ID NAT technology plays a critical role in responding to the public interest in non-discriminatory criteria and is crucial in terms of how to interdict pathogens, and thereby improve the safety of the blood supply and protect patients."

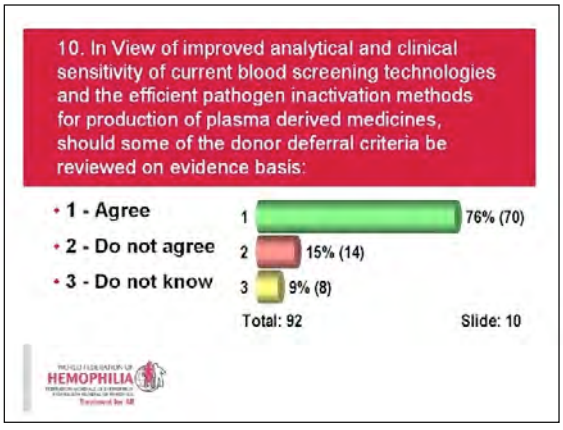
A participant noted that the audience poll showed that 54% did not feel the lifetime deferral for MSM donors is justified; and 54% also said there isn't sufficient information for a change in deferral. "My main concern is that once again we are seeing decisions being made based on politics and not on scientific evidence," he said. "Patient communities would accept reasonable changes to donor deferrals that are based on scientific information and studies." Dr. Kleinman agreed that a scientific basis to decision-making is of paramount importance but said problems arise with extremely small risks. These require modelling and the assumptions put into the model can drive the outcomes. So long as there isn't zero risk, there will be a subjective element to decision-making based on value judgments on risk level and donor deferral.

Another participant pointed out that viral inactivation reduces but does not eliminate parvovirus B19 from plasma products and asked whether mini-pool testing is adequate against non-enveloped viruses. Dr. Kleinman said that there could be better inactivation processes for such viruses but the challenge is that very sensitive screening of parvovirus B19 would result in much more plasma being discarded. The modelling indicates that final products need to be screened; most manufacturers screen the input plasma.









Session 2: Health Technology Assessment in Hemophilia

CHAIR: BRIAN O'MAHONY, CHIEF EXECUTIVE, IRISH HAEMOPHILIA SOCIETY

Health Technology Assessments in Hemophilia: An Update

Brian O'Mahony outlined the challenges of applying conventional health economics such as health technology assessments (HTAs) to hemophilia because it is a rare bleeding disorder and lifelong condition with a range of impacts on children and adults throughout their lives; and the inadequacy of some types of health economic measures in assessing the actual impacts, benefits, and outcomes of hemophilia therapies. His talk focused particularly on prophylaxis, which is one of the areas being looked at in the ongoing HTA in Sweden, and highlighted the importance for the hemophilia community to actively engage in such processes and collect outcomes data.

It is well known within the hemophilia community that prophylaxis has proven efficacy as a treatment for hemophilia. It is also well established scientifically that early prophylaxis can decrease the risk of inhibitor development, and that prophylaxis can turn severe hemophilia symptoms to moderate hemophilia and increase a patient's quality of life (QOL) and life expectancy. Equally as important, it can change the individual's perception and experience of living with hemophilia. The quality-adjusted life year (QALY) cost of prophylaxis in hemophilia can sometimes seem unreasonably high but the impact of a bleed or number of bleeds on a joint must be clearly understood by healthcare funders. "What appears to be a small improvement in quality of life using a QOL scale can in fact be quite dramatic in everyday living," he noted.

There are many factors that affect the incremental cost effectiveness ratio (ICER) in prophylaxis:

- data collection methodology and the time period during which it is collected;
- assumed cost per unit of treatment product (factor concentrates);
- assumed number of bleeds per year using on-demand therapy;
- discount rate applied to future health benefits from current therapy.

Treatment is often framed or conceived in terms of the current benefits; in hemophilia, prophylaxis provides children with long-lasting benefits and better physical health and quality of life in adulthood. "A child with hemophilia treated with prophylaxis gets a definite current benefit but it's also transforming his future in a major way. This is usually not taken into account sufficiently by health economists when setting discount rates," Mr. O'Mahony said. The published literature shows an enormously wide range of incremental cost per QALY estimates of FVIII prophylaxis in children from US$50,000 up to US$2.7 million.

Mr. O'Mahony described his recent survey, conducted with his colleague from the Irish Haemophilia Society, Declan Noone, which looked at the quality of life of young men with severe hemophilia in four European countries (Sweden, U.K., Ireland, France). The study collected data from 58 young men with severe hemophilia and compared outcomes with prophylaxis, on-demand, or combined treatment. The findings from Sweden, the only country where prophylaxis treatment for the group surveyed began at two years of age and continues throughout life, showed a perfect 1.0 median quality of life index for the young men, better than that of the general population, and much fewer bleeds (3 per year) and missed school/work days per year. In the U.K., Ireland and France, where prophylaxis was begun later or combined prophylaxis and on-demand treatment were used, there were significantly more bleeds (16 to 20 per year) and missed school/work days. The data is compelling and the survey will be extended to another eight countries, he said.

Experiential data from a case in Germany showed the benefits of prophylaxis in adulthood. The study by Schlenkrich and Chubert was presented in a poster at the 2010 WFH Congress. It compared the outcomes of an adult patient with severe hemophilia and pre-existing joint damage who received on-demand therapy in 2008 and prophylaxis in 2009. While prophylaxis resulted in a 16% increase in factor use (from 164,000 IUs to 191,000 IUs), there was an 86% decrease in bleeding episodes (from 29 bleeds down to 4 bleeds) and an 84% decrease in missed days of work (from 31 to 4 days). An economic extrapolation of this evidence, assuming cost of factor of €0.70/unit and assuming QOL on prophylaxis increased from a score of 0.70 to 0.90, found that the incremental cost of a full QALY is €94,500. Prophylaxis results in 25 less bleeding episodes; the cost per bleed avoided is €756.

Other studies show the impacts of prophylaxis in the prevention of a single bleed. Experiential data was gathered from three adult patients with hemophilia in Ireland; one on prophylaxis with no bleeds, one who had a single joint bleed, and one who experienced a severe iliopsoas bleed. The patient on prophylaxis had a QOL score of 1, the patient with a single bleed had a QOL score of .587, while the patient with the severe bleed had a score of -0.095.

Mr. O'Mahony suggested that rather than comparing the incremental cost effectiveness ratio (ICER) of hemophilia therapy to standard medical interventions, it would be more appropriate to compare it to blood safety interventions. In an HTA, the cost per QALY of prophylaxis (€36,000 – €304,000) does not compare favourably to the cost per QALY of HPV vaccination (€17,383). It is, however, significantly less costly than NAT testing of whole blood donations for HIV, HBV and HCV (€4.3 – €9.1 million), pre-operative autologous blood transfusion (€170,000 – €16.6 million), and post-transfusion HBV testing with the enhanced sensitivity HBsAG assay (€47 million). All of these other measures have been implemented, he noted. The provision of safe and effective therapy prevents blood-borne viruses such as HIV and HCV, the greatest causes of mortality in the hemophilia population in developed countries. The current increased concern over costs of treatment may—but should not—limit available therapy. As for the MSM donor deferral debate, he emphasized, "The provision of optimal care is a duty owed to this community due to the tragedy of past practices."

The Irish health authority recently completed an HTA on prion filtration of red cell concentrates to reduce the risk of variant Creutzfeldt-Jakob disease transmission in Ireland, which determined that the cost would be €11 million annually and would prevent two deaths over a 10-year period; 19.4 discounted life years would be gained; and the incremental cost effectiveness ratio per life year gained would be €2.6 million. The assessment makes it unlikely that prion filtration will be implemented but has led to concern being raised in Ireland about whether blood transfusion safety is being compromised by lack of investment in measures to reduce risk, and whether expensive new technologies to prevent emerging threats are essential to ensure safety despite the high costs and current funding constraints.

Recently, the Swedish Council on Health Technology Assessment (TLV) conducted a systematic review of hemophilia and VWD treatment, in which they reviewed thousands of abstracts and studies (including long-term effects, bypassing agents, and immune tolerance). The expert group found that the evidence is insufficient in all major areas and studies are mainly observational. "For a rare condition like hemophilia, it will not be possible for the evidence to be sufficient in a Cochrane type scenario," Mr. O'Mahony noted. Still, the expert group concluded that there is much to suggest that it is good to start prophylaxis early and it would be natural to extend prophylactic therapy into adulthood. It recommended the creation of a national treatment registry and systematic and centralized follow-up to document the long- and short-term treatment effects, and highlighted the need for more outcomes data.

The TLV has formed an evaluation team (a medical evaluator, lawyer, and health economist) which is now in the process of conducting the Swedish HTA of hemophilia therapies. Only FVIII is being evaluated; nine product brands will be reviewed in terms of their efficacy and reimbursement. The HTA will likely compare different FVIII prophylaxis regimes, notably the high-dose Malmö regime vs. low-dose Dutch regime, and both prophylaxis regimes to on-demand treatment and no treatment. The Swedish Haemophilia Society will submit their views.

Mr. O'Mahony presented a brief comparison of the Malmö prophylaxis regime treatment versus Finland's combined on-demand and prophylaxis regime, noting the dramatically different outcomes. In Malmö, no patient born after 1980 had undergone joint surgery by 2009; the average quality of life score was 0.84 and 68% of the patients had no missed work days in 2009. In Finland, where the majority of patients are treated on-demand or with secondary prophylaxis, 84% of patients had joint damage. The average quality of life score was much lower at 0.69; 31% had retired early from work due to their condition; and another 32% reported missed work days in 2009.

It is very clear that prophylaxis profoundly improves the lives of people with hemophilia and their families. "With HTAs in hemophilia and prophylaxis, it is incumbent on the hemophilia community to collect outcomes data to demonstrate that prophylaxis in hemophilia clearly works," he said. "At the same time, it is imperative for HTA bodies to look at the role of prophylaxis in the prevention of joint damage and inhibitors, joint surgery, immobility, and loss of employment, the costs saved in later life if these complications are prevented, and the impacts of prophylaxis on quality of life."

Hemophilia and Health Technology Assessment

ALBERT FARRUGIA, VICE PRESIDENT GLOBAL ACCESS, PLASMA PROTEIN THERAPEUTICS ASSOCIATION (PPTA)

Health technology assessment has become an important issue in these times of global financial shortage and funding constraints or cuts in health care, said Albert Farrugia. In developed economies around the world, healthcare costs and total pharmaceutical spending continue to rise steadily; this trend is evident even in countries that have already incorporated cost-effectiveness analysis into their policy decision-making frameworks, such as Australia, Canada, and Sweden. He gave an overview of general approaches to health technology assessment and the various factors, outcomes, and measures that are considered.

Health technology assessments are essentially tools that have evolved as a way to assist policy decision-making in terms of prioritization of healthcare funding and allocations. The term "health technology assessment" encompasses a number of approaches and techniques. They mainly involve systematic evaluation of properties, effects, and/or impacts of healthcare technology, with the main purpose being to inform technology-related policymaking in health care (i.e., reimbursement and prioritization). HTAs are usually conducted by interdisciplinary groups, using explicit analytical frameworks to perform comparative cost and outcome analyses of health therapies and technologies. HTAs vary both between and within countries; they can consist of systematic reviews and economic evaluations of the science, pharmacoeconomic studies, or other more broad-spectrum assessments.

Some of the methodologies applied in HTAs include cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis, and cost-consequence analysis. Most HTAs tend to focus on cost-effectiveness analysis, which calculates cost, in terms of dollars, relative to a health benefit (e.g., number of bleeds avoided, number of life years saved etc.); and cost-utility analysis, which calculates costs relative to the quality adjusted life year (QALY). Decision-making authorities are fond of the QALY because it is "the great leveller." QALY is defined as one year of perfect health.

Therefore, the calculation of the costs and benefits of health technologies in terms of QALY is a very good way of ultimately deriving a prioritization schedule in accordance to a healthcare policy setting and so-called "willingness to pay," Prof. Farrugia said. "It is a way of quantifying relative to perfect health."

Health economists have emphasized that when these instruments are used to assist decision-making and prioritization, the principle objective should be to maximize the aggregate improvement in the health status of the whole of society; and the underlying premise is that for any given level of resources available, society (or the decision-making jurisdiction involved) wishes to maximize the total aggregate health benefit conferred.

It is important to remember that the hemophilia population is very small relative to the general population, and the treatment which gives patients a normal quality of life is rather expensive. Still, blood safety measures such as plasma viral inactivation, mini-pool and individual donor NAT testing, and platelet screening and pathogen reduction have been adopted in different countries despite the high costs per QALY. The cost of mini-pool NAT for HIV, HCV and HBV in the U.S. is approximately $6.1 million per QALY, for example, and there are interventions such as autologous blood transfusion which are even more expensive (i.e., very high cost per QALY).

Generally, healthcare reimbursement authorities, funders, payers, and insurance agencies establish policies and thresholds for willingness to pay and coverage on the basis of the costs per QALY. However, other factors also come into play and have led to some relatively expensive measures and treatments being implemented. Public opinion plays a very important role and science is not the only issue, he said. "Despite the fact that blood safety interventions are costly, most countries have adopted strict blood safety measures because the public have made it clear that they want a blood supply that is as safe as possible and have a willingness to pay, which is often related to how much the measures cost."

Research shows that the public is willing to pay more for some types of interventions. A 2000 Johns Hopkins survey on chronic illness in the U.S. found a high level of societal compassion and willingness to pay for interventions for chronic disorders, and that a majority of Americans strongly support and would pay more in taxes in support of policies for chronic illnesses (i.e., drug benefits, caregiver benefits, long-term care insurance and benefits). It remains to be seen whether this willingness endures in the context of the current global financial crisis, but even so policymakers and funders must bear in mind the public's perspectives on healthcare funding.

Cost-effectiveness studies on prophylaxis published to date have largely consisted of cost-utility analyses to quantify the costs per QALY. Many countries use cost-utility analysis to decide on aspects of pharmaceutical spending and reimbursement, but if this cost per QALY criterion were to be narrowly applied to hemophilia treatment and in particular prophylaxis, funding of these relatively expensive therapies could be unlikely and there would be detrimental impacts on patients, Prof. Farrugia said. "Thankfully it is not—but we know that there are pressures."

Some features of cost-utility analysis are problematic for rare bleeding disorders. The first is the discounting of costs and benefits. "When looking at a treatment given over a long time period or a lifetime, the benefit in the economic analysis in the model is discounted—an intervention which provides future benefit is not given the same clout as something which provides benefit now," he said. "Thus the long-term benefits of prophylaxis for patients, such as less joint damage in later years and fewer surgical interventions, are discounted and this has an enormous effect on the cost per QALY."

The 2009 Miners study on the cost-effectiveness and incremental cost per additional QALY of prophylaxis showed that the U.K. National Institute for Health and Clinical Excellence (NICE) uses a discount rate of 3.5 percent. But if this discount rate is lowered to 1.5% (the rate used in the Netherlands), the actual cost per QALY enters a realm within the agency's actual willingness to pay. "This discount issue is enormously important and we need a policy advocacy measure to persuade the authorities that the models need to be adjusted for rare disorders."

The other issue with cost-utility analysis surrounds the cost-utility measurements used to derive the actual QALY itself. When surveyed, patients with chronic disorders often have tempered and modest expectations of their treatment and discount their therapy to a level that makes it difficult to get a reliable QALY measure. However, he noted that the recent study by Declan Noone and colleagues at the Irish Haemophilia Society extracts a bigger deferential between prophylaxis and on-demand therapy. "It shows how interesting it is that when an actual patient organization shapes an instrument, you can get different results," he said.

The Plasma Protein Therapeutics Association (PPTA) has been working on a new cost-utility analysis for severe hemophilia that is assessing the whole of life. "This is the most complex but most comprehensive model for hemophilia comparing prophylaxis to on-demand ever attempted," he said. The Markov model looks at transitions between different types of health states over a long period of time. The difference with this model is that instead of just assessing joint bleeds, it also considers co-morbidities that affect the soft tissues such as cranial, gastrointestinal, and renal bleeds, as well as inhibitor incidence and other factors that affect mortality. The model also inputs randomized controlled trials that show that the inclusion of prophylaxis decreases the incidence of inhibitors, which has a significant effect on cost of lifelong treatment of hemophilia. The analysis is still underway.

"We are living in difficult times, there is no money, everything is under scrutiny including hemophilia therapies. We will have to fight to retain the levels of treatment achieved, using the tools and instruments favoured by health authorities to provide evidence and accurate assessment of the cost and benefits of hemophilia treatment," Prof. Farrugia said.

Healthcare Reform and Healthcare Economics

DR. J. SANFORD SCHWARTZ, SCHOOL OF MEDICINE & THE WHARTON SCHOOL, UNIVERSITY OF PENNSYLVANIA, USA

Dr. Sanford Schwartz discussed the challenges arising for the hemophilia community due to constraints on healthcare spending, and the opportunities to strengthen the evidence base to better inform policy and practice, ensure quality care, and advance the field. There has been enormous progress in the management and care of patients with hemophilia over the past 35 years; however, treatment is expensive and the times are different now. "The goal is always high-quality, cost-effective, evidence-based medicine but we do not always have the evidence we need for the decisions that need to be made—so we have to be practical and realistic," he said.

Evolving evidence, standards, and initiatives in the U.S. will influence other national blood systems. The research community will have to address some of the methodological challenges. Health care strives to maximize access to care, provide quality care, and constrain costs, referred to as the "iron triangle of health care" because the model is extremely difficult to achieve. "There are many different approaches and systems worldwide and it is relatively easy to optimize two of these areas but almost impossible to optimize all three," Dr. Schwartz said.

Traditionally, decisions for the management of hemophilia and other medical conditions have been based on safety and efficacy, i.e., the benefits and results shown in clinical studies, randomized clinical trials, and epidemiological or registration-type studies. However, such studies also have limitations. While randomized clinical trials at this stage have high internal validity and data reliability with natural adjustment for confounders, they have significant limitations because of the highly selective patient population, the comparators used, lack of adherence to guidelines and protocols, and very limited outcomes set for limited timeframes. In the words of healthcare researcher David Mant: "The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but arguably the worst way to assess who will benefit from it."

As noted by Dr. Richard Kravitz, clinical trials demonstrate the benefit or harm of treatments but often fail to show the complexities in terms of substantial benefits for some, little benefit for many, and harm for few. "As we get more and more into treating sub-populations, this becomes more and more the case. So we need to not only ask 'can it work?' but 'does it work?' and look at how well it works in different groups of patients, under what conditions," Dr. Schwartz said.

This has led to the concept of comparative effectiveness (or relative effectiveness in Europe), which looks at how well a therapy works in comparison to other alternatives and how it performs across various subgroups. The aim of comparative effectiveness is to generate and synthesize evidence that compares the benefits and harms of a medical intervention and alternative methods to prevent, diagnose, treat, and monitor a clinical condition or improve delivery of care. In theory, comparative effectiveness research is focused on patient needs and typical patient care settings. "The goals are to guide evidence-based decision-making—that is, to ask the questions that may not be of high interest scientifically but is information that decision-makers, clinicians, patients, and payers will want to know," he said. "This highlights the importance of communicating risk information effectively to be able to achieve our scientific goals."

Patient-centred outcomes research has several aims:

- Inform clinical decisions regarding screening, diagnosis, and treatment.
- Focus on effectiveness, not efficacy.
- Compare at least two alternatives, one of which may be "usual care."
- Measure outcomes that matter to patients, including harms, benefits, and preferences at both population and subgroup levels.
- Include the generation and analysis of new evidence, secondary data analysis, data synthesis, and data integration.

The United States has established the Patient-Centered Outcomes Research Institute to support comparative effectiveness research, promote evidence-based decision-making, and involve multiple stakeholders (patients and patient advocates, physicians, nurses, hospital administrators, healthcare decision-makers and industry representatives) in an open, transparent process. Despite the constrained economic environment, the institute has dedicated funding; by 2014, the U.S. will be spending $750 million annually on comparative effectiveness studies. The institute will address clinically relevant questions with potential to change practice, impact disease burden, minimize undesirable variation, improve health outcomes across the lifespan, reduce the burden of disease and health disparities, and reduce the costs of treatment.

Increasingly, the absence of evidence of effectiveness is being interpreted as evidence of the absence of effectiveness—this makes it imperative for researchers to generate the evidence that is needed through studies in different settings. In addition to randomized clinical trials, evidence from registries, observational data and patient-reported outcomes will play an important role in pragmatic practice focusing on the relevant patients for the specific recommendations.

Healthcare expenditures globally are growing and consuming an increasing portion of national GDPs. The challenge is not just to cut costs, but to cut them wisely and effectively. This requires looking at cost effectiveness in terms of the benefits and value from multiple perspectives. For hemophilia treatment, it means assessing not just medical costs or costs per bleed but also productivity and quality of life—if these aspects are not measured, they won't be counted. For prophylaxis, it is necessary to focus much more on functional status, intracranial, kidney and gastrointestinal bleeds, and the value of delaying joint replacements. These aspects have not been sufficiently addressed in previous studies.

Incremental cost effectiveness, which measures the additional cost per unit of additional benefit, is also important. However, cost effectiveness does not necessarily mean cost savings—it means getting better value, Dr. Schwartz said. Therefore while clinical trials tend to examine relative risks, policymakers are concerned with absolute risks and absolute risk reduction.

It is time to move beyond the notion that randomized trials are the only acceptable form of research, he said. It will not be possible to attain all the necessary measures in the timeframe available, therefore it is critical to use the right method to answer the right questions. It is also necessary to expand time horizons so that outcomes are measured throughout the patients' lives. Data needs to be compiled and analysed within sub-populations, and incremental data must also be examined. Medical interventions must be assessed using novel analytical approaches, including adaptive trials, indirect comparisons, and confounding adjustment. Assumptions and models must be transparent and flexible, and address issues of generalizability, transferability, and integration of data. Good medical assessments will require a broad range of empirical data including experimentation, observation, synthesis, and modelling. It will also need to incorporate patient-reported outcomes and preferences. All of this data will have to be part of a structured integration of expanded, complex, multi-factorial outcomes. Finally, risk communication is extremely important. To be persuasive, messages must be framed appropriately for the intended audiences so that the information is well understood.

Discussion

A participant asked about how to decide what measures to look at in comparative effectiveness research. Dr. Schwartz said that it is not always necessary to seek precise answers to important questions. "It's important to look at lifelong measures that are important to patients. Efficacy tells us the best we can do, while effectiveness tells us what we are actually managing to do. The goal is to improve research on efficacy and effectiveness, not to do it perfectly."

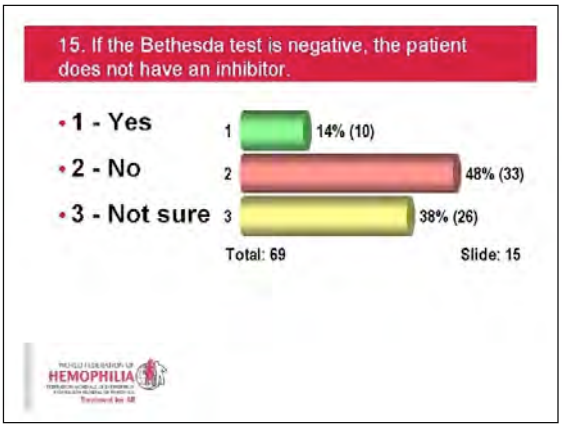
Participants asked about the particular challenges with decision-making related to healthcare coverage for rare diseases, such as the small populations involved, and how some of them could be overcome. Dr. Schwartz said that rare diseases actually have an advantage as it means that potential treatment changes are less likely to draw a great deal of attention. Even a modest increase in the cost of treatment for cardiovascular care would completely swamp the system but hemophilia treatment, even though expensive, will not. To get around the problem of dealing with small numbers, natural experiments can be conducted. If populations are relatively similar, i.e., populations clinically and biologically belong to the same subgroup, multinational registries can be used.

Prof. Farrugia said the evidence for hemophilia treatment is unequivocal. "There was a time when natural outcomes were grim but thanks to prophylaxis, a whole generation has now achieved healthy and functional adulthood. There is no doubt the treatment is effective." Dr. Schwartz replied that natural experiments needn't compare on-demand therapy with prophylaxis; they can look at compliance rates or a myriad of other factors.

Session 3: Update on Inhibitors

CHAIR: MIKE SOUCIE, CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC), USA

Inhibitors are currently a top-ranking safety issue in hemophilia treatment, as reflected in the audience poll at the start of this Global Forum; 54% of participants selected inhibitors as the biggest safety threat today. This session would provide an update on studies related to inhibitors.



How Do We Define A Clinically Relevant Inhibitor?

DR. CAROL K. KASPER, EMERITA PROFESSOR OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA; LOS ANGELES ORTHOPAEDIC HOSPITAL, CALIFORNIA, USA

The question of how to define a clinically relevant inhibitor prompts the corresponding question of how to define an inhibitor that is not clinically relevant; in general, clinically relevant inhibitors are neutralizing antibodies and exclude non-neutralizing antibodies.

Measures of clinical relevance include:

- factor concentrate, in usual doses, does not control bleeding because of inhibitory action;
- *in vivo* recovery measurement is clearly abnormal;
- half-life is clearly abnormal.

In vivo tests are more sensitive than the Bethesda test. One can have a normal *in vitro* result (i.e., negative Bethesda test) but abnormal *in vivo* results that in general are modestly clinically significant. However, it is important to note that even very low level transient inhibitors can be consequential; for example, in one case, a patient who tested normal for factor recovery *in vivo* prior to surgery had profuse bleeding during the procedure and his factor level fell to zero. The patient had a very low level, transient inhibitor that was not detected through *in vivo* testing but was in fact clinically significant in surgery. Thus when possible, it is important to pick up low-level inhibitors, which may seem modest but can be clinically significant.

Half-life is usually described in pharmacokinetic terms and measurement of the second phase or state of catabolic phase, which is about 12 hours. However, an early-phase half-life test is based on its own half-life norms established in order to be able to make the measurements within a clinic day over a 6-hour period.

The Bethesda assay was developed in 1975 by a committee of hematologists with the aim of having a uniform inhibitor test for the United States; prior to this, laboratories in the U.S. each had their own method of inhibitor testing, using different conditions and different definitions of a unit. The parameters of the Bethesda test were very hard fought; consequently, the test was not designed as the most sensitive possible but was rather a compromise acceptable to the members of the committee. When the Bethesda test was first published, the paper was accompanied by a letter to the editor discussing modifications to make the test more sensitive to measure very low-level inhibitors.

In this new era where data is being collected on inhibitors in order to survey the hemophilia population to know how many patients have inhibitors and investigate possible correlations; or to be able to exclude patients with inhibitors from studies (e.g., clinical trial of a new factor concentrate in previously treated patients who do not have an inhibitor). A lot of discussion surrounds the correct cut-off point in the Bethesda test; in fact, the cut-off point in the test is arbitrary. A high cut-off point reduces false positives and a low cut-off point reduces false negatives. It is helpful for a lab to gain experience with definite but low-level inhibitors, e.g., from a patient whose inhibitor is declining with immune tolerance therapy, which may help the laboratory choose the cut-off point that makes the most sense for that lab.

"In my laboratory we followed patients with developing inhibitors as well as eradication of inhibitors in those undergoing immune tolerance induction and thus we were able to assess true inhibitors as they declined and the reliability of the Bethesda test in its specific laboratory conditions using its specific reagents, and establish a cut-off point for our laboratory," Dr. Kasper said. The goal was to detect low-level inhibitors and not have false negatives therefore the cut-off point was set low; a patient who seems over the boundary of the cut-off point can be followed up with another test. However, the cut-off point is an arbitrary decision and in some cases a different cut-off point might be used; for example in a particular study or in the absence of a reference laboratory to perform the test, wherein the local criteria for an inhibitor would need to be used.

Update on Two Inhibitor Studies

DR. ELENA SANTAGOSTINO, ANGELO BIANCHI BONOMI HEMOPHILIA AND THROMBOSIS CENTER, IRCCS MAGGIORE HOSPITAL AND UNIVERSITY OF MILAN, ITALY

Dr. Elena Santagostino provided an update on two initiatives on inhibitor development in patients with severe hemophilia: the Study on Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) and the European Haemophilia Safety Surveillance System (EUHASS).

The SIPPET Study is a randomized clinical trial involving severe hemophilia A patients which is investigating the role of type of product in risk of inhibitor development. Patients are randomized to receive a product from one of two classes (recombinant FVIII products not containing VWF or plasma-derived products containing VWF) and followed up for 50 exposure days. The inclusion criteria are:

- children with severe hemophilia A less than six years old;
- negative for inhibitors at screening;
- previously untreated patients (no exposure to any blood product);
- patients minimally exposed to blood components (less than five exposure days to blood components, i.e., whole blood, fresh frozen plasma, cryoprecipitate, or red blood cells).

Any factor concentrate exposure leads to exclusion.

The study's target sample size is 300 patients in order to provide 80% power to detect a significant difference; this calculation was based on the assumptions of 25% cumulative inhibitor incidence in patients treated with recombinant FVIII products and 50% lower incidence with plasma-derived FVIII/VWF products.

There are 23 countries involved from around the world; 14 countries are already recruiting patients and 3 more countries are ready to begin, and the trial is pending approval in 6 countries. Thus far, there have been many patients recruited in India and Egypt; recruitment in India was recently decreased in order to allow the other countries to recruit more patients and have a more balanced study population. To date, 153 patients have been recruited, of which 107 patients have been exposed to treatment and 31 patients are awaiting their first exposure within the study. There were 11 screening failures, 12 patients who dropped out before exposure, and 5 patients who dropped out after exposure. So far, 13 cases of inhibitors have occurred and 18 patients have completed the study. A utility analysis will soon be carried out, when 150 patients have been exposed to FVIII for at least 20 exposure days.

Some possible limitations of the SIPPET study are that product brands are considered as belonging to one of two classes (recombinant or plasma-derived FVIII/VWF); and the inclusion of minimally exposed patients to blood components. It is known that the risk factors and pathogenesis of inhibitors in minimally exposed patients may be somewhat different; some subgroup analysis has been performed in this patient group.

Among its strengths, SIPPET compares recombinant and plasma-derived FVIII products within the frame of current clinical practice; and the patients enrolled are treated on prophylaxis or on-demand regimes according to investigator preference (the tendency is different in different centres and different countries; on-demand is still the most widely used regime worldwide). The larger, global recruitment platform will be an advantage because the study results will be applicable to all patients with severe hemophilia A worldwide and not only patients living in a specific geographic area.

The European Haemophilia Safety Surveillance System (EUHASS) was initiated in 2008 to track adverse events in previously untreated patients (PUPs) and previously treated patients (PTPs) with hemophilia, von Willebrand disease (VWD), and rare bleeding disorders. A number of sentinel centres in Europe report all adverse events associated with the use of clotting factor concentrates prospectively using an electronic reporting system. The system monitors a range of adverse events such as inhibitor occurrence, transfusion-transmitted diseases, infections, allergic reactions, thrombosis, malignancies, and deaths.

Data reported by the sentinel centres is event specific; the centres are obliged to report inhibitors every three months but in practice this is usually now done in real-time. When an inhibitor is reported to EUHASS, additional details about the inhibitor development and treatment history are requested. Cumulative data is collected on an annual basis such as number of patients treated with specific brands of factor product and number of PUPs at each sentinel centre reaching 50 exposure days without inhibitor occurrence, which enables the calculation of the incidence in PUPs.

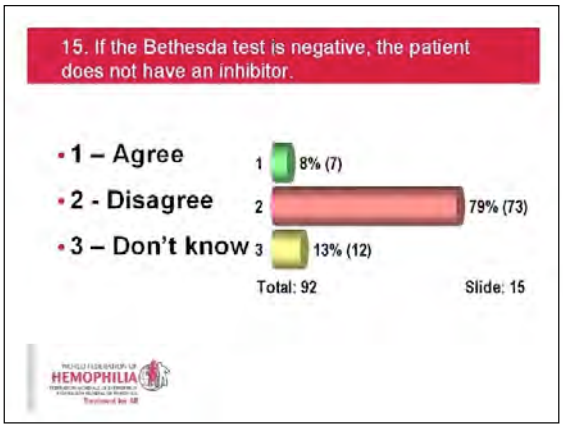
The aim is to collect epidemiological data on inhibitor incidence (cumulative incidence or rate) and incidence according to product. The challenge is that this is not a usual cohort study, in which patients enter at first exposure day and are followed up for 50 exposure days; EUHASS follows a dynamic cohort in which patients are registered when they reach the endpoint, i.e., when they develop inhibitors or reach 50 exposure days. All sentinel centres are performing the inhibitor assay according to the omega modification; an inhibitor should be confirmed on two consecutive samples locally.

There are currently 23,811 hemophilia A and B patients under surveillance at 64 hemophilia centres in 27 European countries. Findings to date include:

- During the first two years of surveillance, 83 new inhibitors were reported: 40 in PUPs with severe hemophilia, 18 in PTPs with severe hemophilia, and 25 in mild and moderate hemophilia patients. The incidence of inhibitor development in PUPs with hemophilia A was 25% and in hemophilia B was 4%.
- The incidences of inhibitors according to the use of plasma-derived or recombinant products are similar; however, the confidence intervals are wide therefore additional patients and longer surveillance are needed to obtain data that is significant.
- There are some differences in inhibitors in PUPs by different brands of recombinant products but the confidence interval is very wide, thus more data is needed.
- Among PTPs with severe hemophilia who have reached more than 50 exposure days, inhibitor incidence is 2.3/1,000 in hemophilia A and 1.6/1,000 in hemophilia B.
- The majority of PTPs with a large number of exposure days prior to inhibitor development had a low titer at first detection; longer follow-up is needed to ascertain whether the inhibitors remain low titer.
- There have been 25 inhibitors reported in patients with mild and moderate hemophilia; 11 in moderate hemophilia A and 14 in mild hemophilia A. No inhibitors have been reported in mild and moderate hemophilia B.
- The median age of inhibitor detection was 44 years; more than half of these inhibitors developed prior to reach 50 exposure days.

To date EUHASS has found no differences between concentrates. The plan is to continue surveillance and monitoring of inhibitors and other adverse events, and recruit countries and centres outside Europe to participate; there are currently 75 European centres involved and Canada and Australia will soon be joining the initiative. A three-year report will be completed in early 2012. In addition, EUHASS is taking steps to prepare for monitoring new products with prolonged half-life.

The audience was polled again on whether a negative Bethesda test means the patient does not have an inhibitor. This time, 78% of participants disagreed with the statement, compared to 48% in the original poll at the start of the session.



Update on U.S. Hemophilia Inhibitor Research Study

MIKE SOUCIE, ASSOCIATE DIRECTOR OF SCIENCE, CENTERS FOR DISEASE CONTROL AND PREVENTION, USA

The Hemophilia Inhibitor Research Study in the U.S. started out as a pilot test to determine the feasibility for national inhibitor surveillance according to the guidelines published by the European Medicines Agency (EMA) in 2006. The guidelines called for:

- centralized inhibitor testing or very strictly quality-controlled inhibitor testing;
- centralized genotyping;
- prospective collection of product exposure data to try to address the issue of misclassification due to patient recall issues.

Phase II of this study is now underway with several aims:

- *Arm 1:* Increase the database on product exposure data; develop nationwide mutation database, i.e., CDC Hemophilia A Mutation Project (CHAMP).
- *Arm II:* Increase genetic data on patients with a history of an inhibitor.
- *CHAMP:* Immune response gene testing.

The pilot study included more than 100 patients with a previous history of inhibitors. A second arm has been added in Phase II with the goal of increasing the enrolment of patients with a history of an inhibitor to be able to look at the relationship between previous history and inhibitor mutations. In the U.S., unlike some places in Europe, a minority of patients have been genotyped, therefore, there is still a lot to learn in terms of the different types of mutations that occur in the U.S. hemophilia population and their associations with inhibitors. Immune response gene testing is being performed and the novel mutations are being entered into a national database as part of CHAMP.

The study has made good progress on its objectives:

- *Patient enrolment:* There have been 17 hemophilia treatment centres involved; 1,167 patients were enrolled in Arm 1 and 11 additional patients with a previous inhibitor history have been added as part of the recently started Arm 2.
- *Inhibitor testing:* Nearly 3,000 inhibitor tests have been performed in collaboration with the Universal Data Collection (UDC) project; testing is done on annual basis, prior to a planned product switch, or in the event that a patient has clinical indication of inhibitors.
- *Databases:* Since 2006, a large database of product exposures has been amassed, with close to 100,000 infusion logs, which will yield a wealth of information on patients with hemophilia in the U.S., the way products are used in clinical care, and baseline information and comparison data for broader nationwide surveillance.
- *Genotyping:* Testing has been done on 137 patients with a previous history of inhibitors and 1,041 patients with no inhibitors. So far, 248 unique *F8* gene mutations have been identified that were not previously reported elsewhere; 62 unique *F9* gene mutations have been identified that were not previously reported. Data collected also reflects a higher rate of inhibitors among African-American and Hispanic patients; the increased inhibitor frequencies in these patients do not appear to be caused by differences in *F8* gene mutations present and the preliminary data suggests that product mismatch does not play a role in higher inhibitor frequencies. The study of immune response genes could potentially lead to information on the difference in occurrence rate in these populations.

A modified Nijmegen-Bethesda assay was adopted for the study given the aim to use the inhibitor test as part of national surveillance when patients come in for their clinic visits; the modifications were needed to account for the fact that patients often will have had a recent factor infusion per their treatment regimen. This involved:

- Split sample comparison showing that shipment on cold packs, which is much simpler on a nationwide basis, is equivalent to frozen specimens (provides just as good results).
- Heating step to remove infused and endogenous factor VIII.
- Effectiveness was confirmed by absence of FVIII activity and antigen in heated specimens.
- Co-efficient of variation (CV) was 10.3% for the positive control; 9.8% for the negative control.
- Cut-offs were established by comparing results on patients with negative history of inhibitors to those with positive history.

The investigators were able to identify a range between 0.4 and 0.6 that distinguished very well between patients who were negative or positive for inhibitors; a threshold of 0.5 Nijmegen-Bethesda Units (NBU) was set for a positive FVIII inhibitor. About 60% of the patients with a positive history tested negative at enrolment due to successful immune tolerance induction or treatment with bypassing products. Examination of all inhibitor titer specimens confirmed the range of values and the cut-off set at enrolment. There were only two patients with hemophilia B with previous history of inhibitors; the threshold for a positive FIX inhibitor was set at less than 0.2 NBU.

The CDC Hemophilia A Mutation Project (CHAMP) was developed to provide an aid for genotype analysis and reporting, including a comprehensive updated list of the mutations identified in the U.S. and mutations being reported elsewhere around the world. The investigators gathered information on mutations from the Haemophilia A Mutation, Structure, Test and Resource Site (HAMSTeRs) database and through a systematic literature review. Each mutation found was reviewed and uniquely identified using both the HGVS nomenclature for cDNA and predicted protein changes as well as traditional nomenclature based on mature processed protein. Of the 2,142 mutations that have been reported, 1,091 are missense mutations (more than 50%); 294 missense mutations have been associated with inhibitors, representing about 18% of patients reported with inhibitors.

The CHAMP website contains a database of reported mutations and their unique identifiers, which is updated quarterly based on submissions from scientists engaged in mutation analysis around the world and literature reports. Two additional databases are being planned to gather more data on mutations reported in the U.S., and population-based mutation and inhibitor data from defined geographic regions worldwide to determine if there are particular mutations that are more common in various regions. This may shed light on some of the issues in terms of differences in mutations and inhibitor rates.

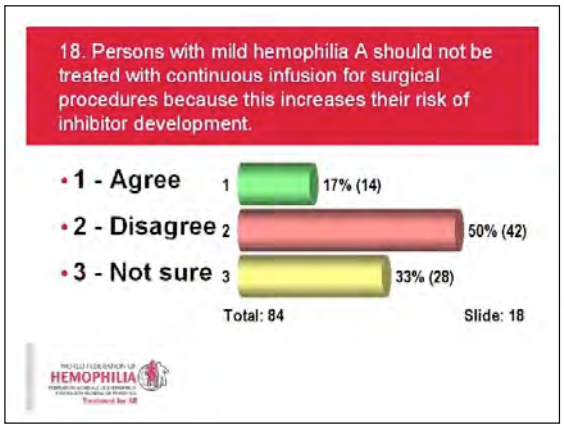
Currently there is no national surveillance for inhibitors in the U.S. and reporting of inhibitors by clinicians to the FDA MedWatch system appears to be inconsistent—however, surveillance is very important with new products coming onto market. The pilot study led to several recommendations for national inhibitor surveillance:

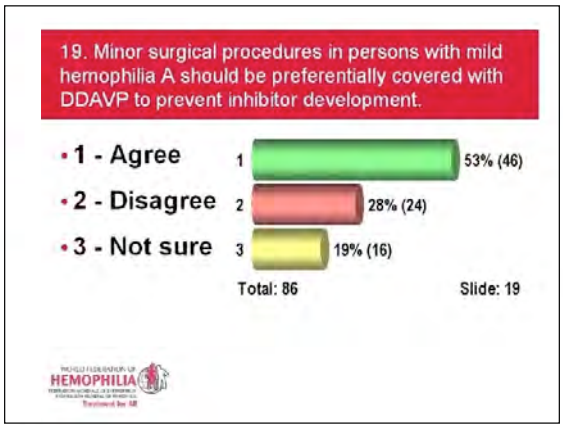
- routine monitoring of all hemophilia patients for inhibitors in a centralized laboratory as part of national surveillance in order to have consistent inhibitor titer measurements;
- case surveillance for incident cases;
- retrospective investigation of cases of new inhibitors (retrospective data collected on product exposure and surgical/outpatient procedures from one year prior to detection).

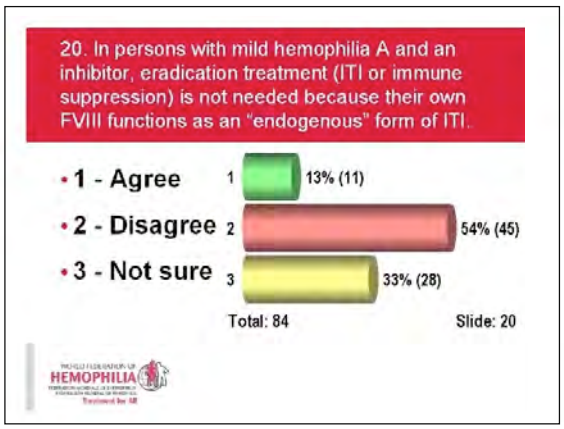
Monitoring of inhibitors should focus on trends in occurrence over time, demographic and geographic sub-populations as necessary, and clusters or "outbreaks" of inhibitors that might be associated with either genetic mutations or new products coming on the market. Monitoring inhibitors through UDC surveillance could identify many more inhibitor incident cases. Benefits include:

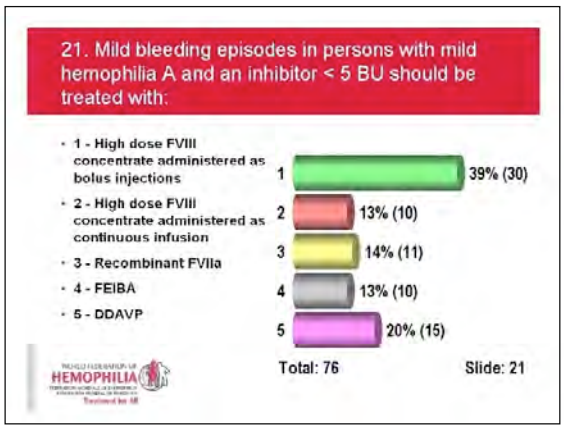
- Data collection is more focused and requires less time-intensive work at the HTCs than gathering the data prospectively.
- Risk factors and their interactions can potentially be determined in a shorter time period.
- Collection of data comparable to the European Union Haemophilia Safety Surveillance System would facilitate future international data comparison on inhibitors, e.g., through combination of data and harmonization of data to be able to answer the questions more quickly.

Genotyping of incident cases is important but may be cost-prohibitive at the national level; funding support will be sought from the hemophilia community and other organizations.









Inhibitor Development in Mild/Moderate Hemophilia A

DR. CORIEN ECKHARDT, PEDIATRIC HEMATOLOGY, ACADEMIC MEDICAL CENTER, AMSTERDAM, THE NETHERLANDS

Dr Corien Eckhardt presented the first results of the international Insight Study on inhibitor development in mild and moderate hemophilia A, led by Dr. Karin Fijnvandraat. Inhibitor development in mild and moderate hemophilia patients is a very serious complication. Indeed, the impact in mild and moderate patients may be even more severe as it is possible for the inhibiting antibodies to not only render the infused factor concentrates ineffective but also neutralize the endogenous factor VIII, which could result in a decrease of the FVIII plasma levels to below 1% and severe bleeding complications in patients who are not trained for home treatment.

Moreover, there is no literature on how to treat mild and moderate patients with inhibitors for bleeding or surgery, nor on how to eradicate inhibitors in these patients. A national study in the Netherlands by Iris Plug et al. and the preliminary EUHASS results both indicate that about one-third of all new inhibitors develop in mild and moderate patients. Thus inhibitors are a severe and substantial problem in the treatment of mild and moderate hemophilia but remain a neglected area of research.

The Insight Study was designed in 2007. There are currently 34 participating hemophilia treatment centres (HTCs) across 10 European countries and Australia, and about 2,700 patients in total. Three main studies are being done:

Cohort study: Clinical data (FVIII genotype, plasma levels, family history, viral infections, and mortality) has been collected on 2,700 mild and moderate patients who were treated between 1980 and 2010. Preliminary results were presented at the 2011 Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Kyoto, describing genetic risk factors for inhibitor development, inhibitor development and mortality, cumulative incidence of viral infections and its complications and related mortality, and the relation of F8 genotype and FVIII plasma levels. The primary aim of the cohort study is to investigate the association between F8 genotype and inhibitor development in a large unselected international cohort of patients with mild and moderate hemophilia A, on the hypothesis that missense mutations in the light chain and/or caused by cysteine replacement are associated with an increased risk for inhibitor development. The cohort study is the source population for the nested case-control study.

Nested case-control study: Clinical data and DNA samples of the 100 inhibitor patients detected in the cohort study and 400 controls matched for cumulative exposure days have been collected. The control group data is especially important in mild and moderate hemophilia because most patients are treated on demand, which means that even adult patients can have less than 50 exposures to factor VIII and still be at risk to develop inhibitors. Analysis of the data will be done this year and the results are expected at the beginning of 2012.

Satellite study: The Treatment of Inhibitors in Mild/Moderate Hemophilia A (TRIM) Study collected additional data on the 100 inhibitor patients on treatment during or after inhibitor occurrence (DDAVP, NovoSeven, FVIII concentrate) and inhibitor eradication therapy. Preliminary results were presented in a poster at the 2011 ISTH Congress.

There are several main findings so far:

Genetic risk factors for inhibitors: 1,300 of the 2,700 patients in the cohort study were genotyped including 80 inhibitor patients; more than 95% of the inhibitor patients had a mutation in two specific regions, the light chain of the F8 gene and a small region of the A2 domain. The investigators analysed the absolute risk of the F8 genotypes and adjusted for cumulative exposure because a majority of the patients have had less than 50 exposure days. Patients who had F8 gene mutations in these two specific

regions were found to have a fivefold increased risk for inhibitor development compared to patients who had mutations outside these regions. Cysteine replacement, which causes missense mutations in the light chain, was associated with a twofold increased risk for inhibitor development. Family history of inhibitors was also associated with increased risk, independent of the patient's F8 genotype.

Mortality in mild and moderate patients: Inhibitor development was associated with much higher risk of all-cause mortality—more than twofold greater than for non-inhibitor patients. The major causes of death in the mild and moderate patients with inhibitors were malignancy (25%) and bleeding (19%).

Treatment of inhibitors: The TRIM study found that 74% of the mild and moderate hemophilia patients who had developed an inhibitor needed treatment for bleeding or surgery during their inhibitor episode. Inhibitor eradication therapy by immune tolerance induction or immunosuppressive treatment was initiated in 28% of the inhibitor patients and was successful in about 68%. Among patients who did not receive inhibitor eradication therapy, the inhibitor disappeared without eradication therapy. The data on inhibitor eradication therapy and treatment of the patients will be further analysed in the coming months towards gaining insight on the best treatment to eradicate the inhibitors as well as how to treat inhibitors during bleeding and surgery.

Future research will focus on three areas: prediction of inhibitors, prevention, and treatment. In terms of prediction, investigators will look at environmental risk factors and the role of intensive treatment and surgery in these patients; analyse the F8 mutation data already collected and DNA samples for genetic variations in immunoregulatory genes which may be associated with inhibitor development; and examine the interaction between genetic and environmental risk factors. The investigators hope to develop a clinical prediction tool to estimate inhibitor risk in individual patients.

Another aim is to explore the development of preventive strategies such as prophylaxis to tolerize mild and moderate patients (instead of to prevent bleeding), immunosuppressive medication, or treatment with other medications such as bypassing agents in high-risk situations or patients. There are currently no tools to prevent inhibitors in mild and moderate patients.

Finally, research will also focus on distinguishing the best treatment strategy when patients have developed an inhibitor. There is need for standardized guidelines for prevention and treatment of bleeding and inhibitors in mild and moderate hemophilia A patients.

Discussion

Investigators are clearly engaged in extensive efforts to address the issues and challenges of inhibitors, and the multiple dimensions of inhibitors and various epidemiological analyses were all discussed during the session, said session chair Mike Soucie. A participant noted that at the start of the session, the audience was polled on which is the most important patient group to study in order to identify risk factors for inhibitors, previously untreated patients or previously treated patients. "My understanding has always been that if you want to look at a problem such as potential neoantigenicity in factor concentrates as a result of manufacturing or similar issues, the best patient group is PTPs. But it depends on the research question and what you're specifically looking for—whether it is particular characteristics involving patient genetics, or de novo inhibitors related to a specific product switch." Dr. Santagostino agreed that PTPs are the best patient population for investigating neoantigenicity. However, PTPs can sometimes have very low titer inhibitors and this can complicate studies; in the past their participation in product trials has resulted in the exclusion of a new product from market. Mike Soucie said since we don't really know all the factors, it's important to study both patient populations because there are different risk factors for both groups.

A participant asked whether studies have been done on the influence of childhood vaccination on development of inhibitors in PUPs. Given that a lot of these vaccines include adjuvants to prime the immune system, this could be a factor in sparking immune reaction. Is this being investigated and have there been any conclusions? A few studies have looked into this and found no evidence that vaccination is a risk factor in PUPs, but the issue is inconclusive as the studies involved only a small number of patients, Dr. Santagostino said. In Europe, for instance particularly during immune tolerance induction, treaters try to avoid vaccination on the same day as infusion because it may play a role in some increase of the inhibitor titer. However, this is done on an empirical basis and there is no clear information at this time.

Given that clinical trials for rare disorders involve small numbers of patients, it is very important to have national surveillance to monitor patients over a period of time after the licensure of new products to make sure that the switch does not increase the safety risk, Mr. Soucie said.

A participant said that efforts are being made to create new paradigms for efficient trials on the safety and efficacy of new products, especially given that there are many studies and very few patients. Is there a need to also look into paradigms for post-registration surveillance of the new products, or will systems such as EUHASS and national surveillance mechanisms pick up information on inhibitor occurrence needed to ascertain long-term safety? The annual patient examination system in the U.S. helps pick up inhibitors but it is tough is to know exactly how much treatment the patient has had since the last visit, said Dr. Kasper. A system could be set up but getting patients to take accurate logs is another issue. Mr. Soucie said it is important to collect data not only on the amount of exposures but also the circumstances under which the exposures were given; this is important to evaluating new inhibitors.

Dr. Santagostino said that a preliminary system for post-marketing surveillance already exists, which can be optimized for efficiency vis-à-vis new products; this would be cost-saving and better than running a large number of sponsored Phase IV studies. Investigators are sometimes more compliant with official European or U.S. investigator-driven data collection and less inclined to give the data to companies. This would also provide information on background inhibitor incidence among PTPs overall, which is crucial to making a judgment on a new product during the post-marketing phase.

A participant noted that biosimilars will be entering the market and will require post-market surveillance. Mark Skinner said the WFH is very much aware of the issue and has had some concerns about some biosimilars being developed in less regulatory-controlled environments. There have been examples of bleeding disorder products coming to market without having done clinical trials that would meet the FDA's very high standards. The concern for recombinant products is immunogenicity. The WFH's position has been that one of ways to control for immunogenicity when these products come to market is to ensure that the clinical trials, regardless of where they occur, follow the high standards set by the leading regulatory authorities.

A participant noted that the SIPPET study has enrolled many minimally treated patients. Will this have any effect or will it not matter if they've had five exposures to blood products? Dr. Santagostino said she is convinced that minimally treated patients may be different from true PUPs but it is good to have them on board the study because they exist in clinical practice. "If you ask HTCs around the world how many of their first diagnoses are true PUPs and how many arrived at the centre already exposed to blood components, the majority of new diagnoses are done in patients who have already been exposed at their local hospital—they should be taken into account as a true patient population because they exist." The SIPPET investigators will try to analyse them in a separate manner.

Session 4: Clinical Trial Design

CHAIR: DR. ALOK SRIVASTAVA, WFH VICE-PRESIDENT COMMUNICATIONS AND PUBLIC POLICY

In recent years, clinical trial design has emerged as an important issue in hemophilia in terms of new products for market authorization. At present, there are over 10 new products for the treatment of rare bleeding disorders that need to be evaluated. "The issue has never been as critical as it is now in the hemophilia community," said Dr. Alok Srivastava.

This session presented some of the concepts and challenges of clinical trial design in hemophilia, and the progress of the International Society of Thrombosis and Haemostasis (ISTH) FVIII/FIX Scientific Subcommittee clinical trial design project group towards consensus on definitions and design. In addition, it focused on another important issue in hemophilia, the harmonization of regulatory requirements for product potency labelling, which is being addressed by another ISTH project group.

Through its collaboration with the ISTH, the WFH is able to bring forward these issues for broader discussion by the global bleeding disorders community. The Global Forum is attended by patients, physicians, regulators, and representatives from industry and therefore is a particularly useful opportunity for gathering the spectrum of perspectives.

New Products for the Treatment of Hemophilia

DR. JERRY S. POWELL, DIRECTOR, HEMOSTASIS AND THROMBOSIS CENTER, UNIVERSITY OF CALIFORNIA DAVIS, USA

In the past 25 years, there have been major milestones in treatment for hemophilia, notably the development of viral inactivation processes and recombinant factor and prophylaxis regimes, which have dramatically improved the lives of people with hemophilia, said Dr. Jerry Powell. Now, the hemophilia community is on the cusp of a new breakthrough as long-acting products in clinical development move towards market approval. "This is the most exciting time in a long time and credit is due to the patients and treaters who participate in clinical trials," he said. He described new and changing options in treatment and the impacts on clinical trial design.

It is important to focus on the main goals of clinical trials: safety, efficacy, and patient interest in a new product. Hemophilia is a factor deficiency so it is important to evaluate pharmacokinetic properties, i.e., half-life and factor level. With the new long-acting factors that extend half-life, efficacy can be assessed by measuring the factor level since it correlates with clinical phenotype.

Hemophilia clinical trials over the past 30 years have had a perfect safety record, Dr. Powell said. More than 12 plasma-derived products and over 6 recombinant factor products have come to the market; all efficacy and safety studies involved only a few dozen patients. "A lot of data in clinical research is extraneous to the goal of clinical trials on new products, which is to obtain regulatory agency approval to put the product on the market," he said. "Other hypotheses and research can be done later as part of the post-marketing surveillance."

The goal is to stay focused on efficacy and safety. In previously treated patients (PTPs), a key measurement of efficacy is the patient's assessment of the therapy (excellent, good, mediocre, or none). Simplicity of trial design with minimal intrusion upon patient lives is essential; this means identifying the critical parameter to measure and collecting only critical data (minimal details of bleeds, no clinical scores, no quality of life data, no personal information).

Up until the 1960s, people born with hemophilia had a much shorter life expectancy than normal. Prolonged and recurrent bleeding caused problems such as joint damage and trauma to vital organs that were life-threatening; head bleeds, for example, often resulted in brain damage or death. Many did not survive childhood and most died by early adulthood. This changed after scientists gained knowledge about the clotting factors and realized their goal to develop factor replacement therapies. In the 1990s, aggressive on-demand treatment dramatically improved life expectancy although head bleeds remained a serious risk and joint damage still occurred later in life. Today, prophylaxis is available as preventative treatment. Hemophilia trials have had no safety concerns and have led to normal life expectancy for patients. "No other genetic disease has achieved this tremendous progress, which is due to our educated, enthusiastic patients and the simplicity of clinical trial design," he said.

New products for hemophilia now in clinical trials include same factor molecules produced by new manufacturing processes, altered factor molecules with extended half-life, and biosimilars. When there is minimal molecular change, as with the novel factor Fc fusion proteins which covalently link an immunoglobulin molecule to factor, there is theoretically no reason to suspect that there will problems, Dr. Powell said. This is an example of how the community can make much better progress by moving forward with simple clinical trial design, he suggested.

Currently, one of the main focuses of clinical trials in previously treatment patients is inhibitor risk, which is found to occur within the first nine infusions. This suggests that it is not necessary to base inhibitor studies on 50 exposure days—given the low inhibitor rate in PTPs, clinical trials that use fewer than 100 patients are unlikely to capture any cases, he said. Therefore it may be more effective for clinical trials in PTPs to focus on testing safety, and shift the inhibitor question to the post-marketing surveillance, he added.

Novel long-acting factors have shifted the treatment paradigms, but the correlation between factor level and phenotype remains. He put forward these suggestions for clinical trial design and harmonization:

- Enlarge the pool of patients who can participate in clinical trials; in the past, clinical trials used less than 2% factor level for assessment of severe FVIII deficiency but this has shifted to 1% factor level, making 30-40% of hemophilia A patients ineligible for the trials.
- Focus only on factor level in clinical trials and patient assessment of product efficacy.
- Monitor inhibitor formation for 20 exposure days (which is twice the inhibitor occurrence rate in PTPs), rather than 50 exposure days.
- Assess number of days of factor level above 10% since the exposure day might not be the same day of infusion.

ISTH Clinical Trial Design For Hemophilia Project Group

DR. DONNA DIMICHELE, CHAIR, CLINICAL TRIAL DESIGN PROJECT GROUP, ISTH FVIII/FIX SCIENTIFIC SUBCOMMITEE

The ISTH FVIII/FIX Scientific Subcommittee formed the clinical trial design for hemophilia project group in early 2011 to address pragmatic and regulatory issues related to the safety, supply, and availability of treatment products. Dr. Donna DiMichele described the progress so far towards consensus on how to resolve the issues. From the pragmatic standpoint, several issues in the current context need to be addressed. Multiple products are entering into pre-registration clinical trials at this time. The availability of hemophilia patients for clinical trials is limited given current regulatory enrolment requirements; this issue is amplified in product trials for even rarer disorders. Industry, regulators, clinicians and patients are demanding trial simplification without compromising safety/efficacy assessment.

There are currently variable requirements between regulatory agencies for pre- and post-registration safety and efficacy assessment of clotting factor concentrates. There is broad agreement on the value of discussing and harmonizing regulatory requirements among major regulators. "The underlying philosophy of ensuring the safety and efficacy of biologics is well appreciated, but the scientific basis for many requirements unclear," Dr. DiMichele said.

The project group's mandate is to determine the optimal prospective pre-licensure and observational post-licensure trial designs for new factor concentrates for hemophilia based on: harmonized safety and efficacy data required by regulators for product registration and by the hemophilia community at large post-licensure; anticipated available study population; and innovative clinical trial design suitable for rare diseases such as hemophilia.

Good clinical outcomes definitions already exist and patient-reported outcomes are most valuable in assessing response to treatment. In clinical trial design, it is important to understand the impact of a clinical severity definition based on a threshold of 1% instead of 2% factor level. Other important definitions are inhibitors, bleeds, and response to treatment.

The project group has identified several key aims in order to advance clinical trial design:

- Review current endpoint definitions and clinical trial requirements with guidance from all stakeholders: ISTH FVIII/IX Scientific Subcommittee Definitions Project Group, U.S. and European regulators, industry representatives, scientific and methodological experts, and clinical investigators.
- Develop or refine consensus clinical outcome endpoint definitions (clinical severity, prophylaxis, inhibitors, bleed event, response to treatment).
- Optimize clinical trial design requirements (numbers and types of subjects for safety, efficacy, and surgery trials; study duration; exposure requirements; and assay methodology, e.g., inhibitor and global hemostasis assays).

The next steps are to apply alternative clinical trial design and statistical modelling to five types of PTP (and potentially PUP) trials: FVIII biosimilar and novel biologics; FIX biosimilar and novel biologics; FVIII/IX novel bypassing agents. Input from the FVIII/FIX Scientific Subcommittee was solicited at the ISTH meeting in Kyoto, and industry input will be solicited during this next phase.

To date, the group has noted several challenges for pre-registration trial design optimization:

- Modifying safety rather than efficacy endpoints (especially product neoantigenicity) is the greater design challenge. How much uncertainty is acceptable in pre-licensure regulatory trials and should safety assessment be part of post-licensure observation study? Focusing on safety issues rather than efficacy issues pre-licensure increases trial size.
- There are no alternatives to the traditional inhibitor assay as yet ready for clinical trials; mechanistic studies are needed.
- Unique solutions may or may not be needed for FVIII and FIX products (biosimilar vs. novel biologics) and FVIII/IX bypassing agents.
- The complementary roles of prospective, observational, post-registration studies need to be further explored.

A clinical trial design and statistical modelling subgroup has formed to address the issues. Its tasks are to re-examine PTP immunogenicity clinical trial requirements for FVIII and FIX biosimilars, using currently known neoantigenicity data (applicability to novel products will be further deliberated once early data from first novel factor trials are available); explore potential inclusion of mechanistic

studies into future trials to evaluate other sensitive and biologically representative early detection assays for product immunogenicity; and solicit relevant industry input. In parallel, a subgroup on clinical endpoints and patient-reported outcome measures will liaise with all stakeholders to ascertain precise consensus definitions for relevant and objective clinical efficacy endpoints and patient–reported outcome measures. The data will be incorporated into future project group deliberations on applicable alternatives for clinical trial design methodology for pre- and post-registration efficacy trials. The group will submit a final report to the ISTH FVIII/FIX Scientific Subcommittee in 2013.

Discussion

Discussion focused on several important clinical trial issues: defining the types and numbers of patients that should be included in studies (less than 1% factor level or up to 2% factor level); events to be monitored and recorded for marketing authorization trials (excluding long-term prophylaxis clinical trials); and assessment of responses in these events.

There have been increasing discussions about the problems around 1-2% factor levels and bleeding because there are patients who technically have above 2% factor level who bleed a lot as well as patients with less than 1% levels who don't bleed as much, a clinician participant said. It may be important to look at bleed events or bleeding history rather than factor level around a bleed event. Another problem pertains to patients in developing countries with "spare hemophilia" who may be on prophylaxis and knowing whether they bleed or not.

Another participant said that large number of studies have been carried out and many patients are involved in ongoing trials but given the rarity of hemophilia and the small patient populations, there is a finite number of PUPs to meet the regulatory requirements as well as a danger of patient fatigue. Restriction on the basis of factor level is undesirable not just because it decreases the number of patients available but because the assumption that moderate hemophilia is not as much of a problem is a falsity. "We should construct trials that are able to capture all the patients populations," he said. Trials should be constructed to capture the maximum number of willing patients possible. Factor level alone is not what needs to be measured—clinical trials today also have to include inhibitor assessment. The numbers embedded in regulatory guidances are empirical and have no statistical basis because of the small number of patients, therefore regulators should be amenable to modifications as the occasion demands.

When designing hemophilia trials, there is a lot about patient participation in the trials but it would also be useful to have patients participating in the construction of the trials themselves, a patient participant said. In the HIV community, patient input and representation has been very important in terms of how trials are constructed. The hemophilia community does not engage patients in constructing the trials, even though its patients are often quite knowledgeable; there are patient representatives who have a relatively sophisticated level of expertise and understanding on how to construct trials.

Dr. DiMichele asked if there are specific aspects of trial design where input from the patient community would be particularly important, and whether he agreed with the premise that trials need to be much more efficient, shorter, and smaller going forward and balanced with increased post-licensure data collection. In order to get products out more quickly, would patients be willing to participate in years of post-registration data collection to monitor whether products are truly safe and effective? Patient input is important for all the aspects—in essence, given the limitations of clinical trials versus the real world, there would be real value in having their direct input in the construction process, he replied.

There are also clear payoffs from post-surveillance; patient involvement in constructing the post-surveillance process would improve patient buy-in and data collection. "The community-based research model suggests that patients get fatigued about being asked questions. But if they feel they are actually participating in the research and the long-term value is demonstrated, they're more likely to participate from a long-term perspective," he said.

Dr. Powell said his experience in Northern California is that patients have not turned down participation in a clinical trial unless they are overwhelmed by the complexity of the trial (too much data being collected, arduous quality of life questionnaires, etc.) or because they would not get a stipend for participation. There are different reasons in local communities why patients do not go on trial. However, he noted that there are 14,000 patients with less than 2% factor levels and some 100 clinical trials involving about one-third of these patients. "We're nowhere near the number of patients that can be entered into clinical trial." Another important complexity is that clinical trials over the past 30 years have assessed pharmacokinetics and efficacy but did not count number of bleeds, as it was not registration study criteria. "If we're simply focused on efficacy (does the patient like the product) or safety (are there adverse events) then the number of bleeds is irrelevant," he said. However, companies are now requiring patient bleed records before putting up a clinical trial, because of current regulatory requirements.

A patient representative said patients don't get involved in clinical trials because they are not asked to participate while physicians don't get involved because trials are too demanding and they not have resources. WFH President Mark Skinner added that there are patients who are willing to participate but are excluded because trials now use 1% factor level as the eligibility cut-off. The exclusion of these patients is without good reason and warrants further consideration.

An industry participant said that recently while developing a clinical trial for a biological product for a rare bleeding disorder, his company sought "parallel scientific advice," which is discussion with European and U.S. regulators to try get a common viewpoint before filing a clinical trial application. "It was a very informative and useful exercise and showed that although the advice was parallel, it was not necessary unanimous," he said. "Both regulators are governed by regional regulations or laws that require them to demand certain aspects in clinical trials, so the challenge is probably greater than just reaching consensus—it may involve legislation at the European or U.S. level." He also noted that there are differences in pharmacopeia definitions in Europe and U.S.

Another challenge, which will increase as extended half-life products enter clinical trials, is that the testing period has to be extended in order to look at the pharmacokinetics, requiring greater commitment by patients. The requirement for pediatric studies can also present additional challenges to regulators, manufacturers and patients because it is much harder to obtain blood samples from children in sufficient numbers and quantities for testing, he said.

A patient representative said some patients do not participate in trials because they are satisfied with their current treatment; HTCs are often not interested in the hassle. "It really comes down to making it as simple as possible for patients to understand—the benefits of participation, the amount and length of time involved. If you make it simple, you can inspire treatment centres, nurses and physicians to promote the trial and people will participate."

The greatest challenge for some treatment centres in the U.S. is lack of resources for clinical trials, said a hematologist. Also the complexity of trial design is very hard to understand even for co-principal investigators, let alone patients. In pediatrics, the number of blood draws is the greatest hindrance because they require frequent HTC visits. Patient input is very important when designing trials.

Referring to Dr. Powell's suggestion that factor level endpoints should be enough to establish efficacy, a regulatory official questioned whether trials of the newer novel modified products are actually at a point where they can depend only on factor levels to determine efficacy.

An industry representative said that the 50 exposure days being requested by some regulatory agencies is an arbitrary number. With longer-acting factor circulating in the blood, there is presumably immunogenicity response to the product. However, in trials with longer-acting products, there really isn't an opportunity to explore how long lasting the products are if a patient needs 50 exposure days and each exposure is an injection. In terms of history of exposures for FVIII clinical trials in previously treated patients, the use of 150 exposures is an arbitrary number as well. It is likely grounded in some scientific evidence but as Dr. Powell pointed out the greatest risk of inhibitor formation is in the first 5 to 50 exposures and rarely beyond that. The problem is that regulators, specifically the FDA, have said if more than one inhibitor is detected in a sample size of 80 patients, the clinical trial will be stopped, the results must be noted in the protocol, and that will be the end of the product. "That makes manufacturers apprehensive about making sure that they have adequate records for exposure days since the records can be audited down the road," he said.

In terms of patient-reported outcomes, the patient-rated scale is a bit subjective but at end of day a patient generally knows whether a bleed has stopped or is continuing. If the product is effective at treating a bleed, that will be known and acknowledged at the end of the trial, he said. There is no need to get into much more sophisticated quantitative endpoints that have not been proven in order to get a product license.

Regarding the lack of harmonization between the FDA and EMA, given the costs and complexities of running clinical trials and the limited number of eligible patients, it's not possible to run separate trials in Europe, the U.S., and other countries. "It really requires global studies and this lack of harmonization means that the trial needs to fit a number of different requirements that are an amalgam of regulations," he said. "The latest guidelines from the EMA on FVIII and FIX really are an incredible challenge and will make it so onerous to run clinical trials to get approval in the EU, that it will raises the question of when people in the EU will get access to new products." The EU has gone in the opposite way of what the FDA has promulgated in terms of keeping it simpler, he added.

Potency Assignment of Clotting Factor Concentrates

DR. ALOK SRIVASTAVA, WFH VICE-PRESIDENT COMMUNICATIONS & PUBLIC POLICY

Dr. Alok Srivastava gave an overview of the ISTH Scientific Subcommittee Project Group on Potency Assignment of FVIII and FIX Concentrates, which was formed in 2011. Since the establishment of the WHO First International Standards for Factor VIII in 1970 and Factor IX in 1976, all therapeutic concentrates have been labelled using international units (IUs). In 1993, the ISTH FVIII/FIX Scientific Subcommittee recommended the chromogenic assay for potency assignment of factor concentrates. The European Medicines Agency (EMA) took up this recommendation while the U.S. Food and Drug Administration (FDA) continued to follow the clotting assay for assigning potency. "This difference in regulatory approaches has resulted in certain issues in the community and while this has been recognized, it has not been reconciled," he said.

This issue became evident with the potency labelling for the novel therapy, albumin free B-domain deleted factor VIII. The product was licensed in the United States in 2008 as a new product called Xyntha and labelled by clotting assay; while a variation called ReFacto AF labelled by chromogenic assay was licensed in Europe in 2009. As a result, the 1,000 IU vial of the U.S. product contains

approximately 30% more factor VIII protein than the 1,000 IU vial of European product. The ISTH is trying to address this and other issues at the request of regulators.

Several issues with current practice in potency assignment need to be addressed:

- Most service laboratories use APTT-based assays for assessing recovery after infusion; it can be difficult for them to correlate with products labelled by chromogenic method.
- Issues with assay discrepancies with specific products are often inadequately addressed or left to be resolved at the level of service labs.
- Designing assays for modified FVIII and FIX products with novel structure and/or function (e.g., biosimilars) is a challenge.

There are two guiding principles for potency labelling of factor concentrates: define the quantity of the drug in the vial for manufacturing and marketing purposes; and guide physicians and patients on the product dose to be used to control a bleeding event that would correlate with recovery data measured in clinical laboratories. A key challenge going forward is potency labelling of biosimilar and novel products. "New recommendations for potency assignment should try to resolve assay issues at the level of the manufacturers and regulators and provide clinical laboratories clear guidelines on methodology, reagents and calculation strategies for recovery assays," he said.

The project group's mandate is to find ways to harmonize the recommendations on the methods to use for assigning potency of factor concentrates and make recommendations for assaying post-infusion samples to assess recovery. The group has drafted recommendations on manufacturer responsibilities:

- New products should be tested against the current WHO International Standards for FVIII and FIX Concentrates to establish if valid estimates are possible.
- Factor VIII assays should be performed using both one-stage clotting and chromogenic methods following the ISTH Scientific Subcommittee recommendations and relevant monograph methods (e.g., pre-dilution in FVIII-deficient plasma containing normal VWF; albumin in dilution buffers; specified activation times).
- Evaluation by one-stage clotting method should be performed using different APTT reagents, e.g., silica-based and ellagic acid. It is anticipated that the potency of modified products by the one-stage clotting method may be highly dependent on the choice of APTT reagent in some cases.
- In addition to potency assessment against an appropriate concentrate reference, FVIII assays should also be conducted using a plasma reference standard. This information should not be used in connection with product potency labelling but could be useful when considering the use of a plasma reference standard to monitor the factor VIII recovery of new products.
- Where only one method provides valid tests this could be used for labelling. If there is a potency discrepancy between methods (e.g., one-stage clotting vs. chromogenic) then agreement between regulators and manufacturers on a single method will be necessary.

Draft recommendations on potency assignment of manufacturers' product standards are:

- Whenever possible, in-house product standards should be labelled in IUs depending on valid assays relative to the WHO International Standards for Factor Concentrates.
- Where assays against the WHO International Standards are invalid, it may be necessary to label in arbitrary "product-specific units."

The project group has also drafted recommendations on manufacturer pharmacokinetic studies:

- Pharmacokinetic studies should be performed according to current guidelines (this may require longer sample interval times in the case of long-acting products). *In vivo* recovery should be based on label potency and post-infusion assays against the product standard.
- Assays should be performed using multiple assay systems, i.e., chromogenic and one-stage clotting and, if applicable, with multiple reagents. This stage should also include a plasma standard to see whether or not valid estimates of circulating FVIII or FIX are possible.
- Studies should establish the relationship between dosage, in terms of IUs (or arbitrary units), and the expected FVIII/IX rise in the patient.
- This relationship/dosage key may be assay dependent and should be described in the registration dossier and also in the package insert or other readily available sources in order to inform the clinician of the predicted recovery for specific assay systems.
- This information may need to relate to specific one-stage assay reagents in use in different parts of the world.

The project group noted that the optimal approach to quantification involves testing against a product standard composed of the same material as that infused, but this may be difficult to implement in the routine laboratory. It has drafted recommendations on post-infusion assays in clinical laboratories:

- Routine in-house assays can be used for post-infusion testing providing the local assay system (method and reference standard) is included in the manufacturer's dosage. Robust assay designs incorporating multiple dilutions of post-infusion plasma should be followed.
- The use of a product standard may be indicated by the manufacturer's dosage key when valid assays are not possible using conventional/local standards.

In addition, the project group identified special issues related to clinical definitions:

- What is 1 IU of a modified FVIII or FIX molecule and does the definition of IU apply to such products?
- Does clinical response correlate with recovered factor levels?
- What units should apply to bypassing agents and what is the role of global assays in assessing hemostasis response with such drugs?

Dr. Srivastava invited comments, partcularly from industry representatives, on the recommendations.

Discussion

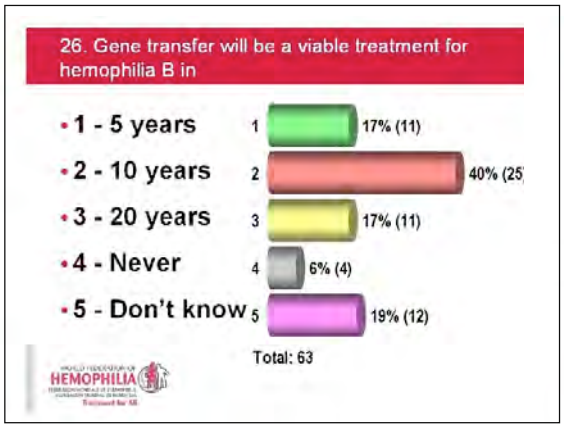
A participant noted that the chromogenic assay only applies to factor VIII as there is no such test for factor IX, which is tested using the activated partial thromboplastin time (APTT) assay. If the claim is that the newer modified coagulation factors are actually the same as the existing ones with a little bit added on or taken off but they do not perform the same assay systems, maybe they are not quite the same, he said. He also noted the difference not only between the products and assay methods but between the standards—that is probably one of the biggest influences on the number derived. Moreover, the only way to ensure that every clinical laboratory has this information is to put it into the product leaflet but it would be a vast amount of information to consider before deciding which one to use. Finally, there might be a 10-20% difference between the assay methods but when it actually comes to dosing in everything except for the clinical trial, how many people actually dose by vial rather than absolute units per kilogram, he said. Dr. Srivastava replied that the APTT and chromogenic assays are surrogates for deciding how to proceed—at the end of the day, clinical efficacy is based on whether a person bleeds or not and whether bleeding is stopped.

DAY 2: SEPTEMBER 23, 2011

Session 5: Novel Technologies

CHAIR: DAVID PAGE, CHAIR, WFH BLOOD PRODUCT SAFETY, SUPPLY, AND AVAILABILITY COMMITTEE

"Really interesting novel technologies and innovations are in the pipeline and possibly close to being ready," said David Page. This session focused on promising initiatives including an ongoing gene transfer study in hemophilia B, and development of solvent detergent technology for viral inactivation of cryoprecipitate which will offer safer treatment for people with hemophilia living in many parts of the world where factor concentrates are currently either unavailable or unaffordable. Presentations from industry described progress with a range of novel therapies for rare bleeding disorders.



Update on Haemophilia B Gene Transfer Study

DR. AMIT NATHWANI, UCL CENTRE FOR STEM CELLS AND REGENERATIVE MEDICINE, UNIVERSITY COLLEGE LONDON, U.K.

The Haemophilia B Gene Transfer Study is an investigator-led study and ongoing clinical trial developed by researchers at the UCL Centre for Stem Cells and Regenerative Medicine (U.K.) and St. Jude's Children's Research Hospital (U.S.), with collaboration by Dr. Mark Kay's gene therapy lab at Stanford University and Dr. Katherine High of the Children's Hospital of Philadelphia.

Hemophilia has long been recognized as an ideal target for proof of concept of gene therapy studies due to a number of factors:

- In hemophilia B, a minute increase in plasma factor IX levels to above 1% following treatment with microgram quantities of factor would be sufficient to ameliorate the bleeding phenotype.
- Strong correlation between factor IX levels and the disease phenotype allows patients to be categorized into severe, moderate, and mild classifications.
- Efficacy can be assessed by validated methods that are routinely available in most laboratories around the world.
- Tight regulation of factor IX expression levels in the bloodstream following factor therapy is not required as there is a wide range of factor IX levels which are likely to be efficacious but not toxic.

Therefore, if gene therapy cannot be achieved for hemophilia B, it will be challenging to accomplish for most other disorders.

Of the available vectors of viral origin, the investigators believe that the adeno-associated viral vector (AAV) is best suited for hemophilia B gene therapy, partly due to its great safety profile. Important safety considerations include:

- AAV is a non-pathogenic single-stranded DNA-based parvovirus that is endemic in humans. Wild-type AAV serotype 2 (AAV2) is highly prevalent; about 70% will have an AAV2 infection sometime during their lives that does not cause illness but results in long-lasting humoral and cellular immunity with the potential to limit efficient transduction with this vector.
- The virus is replication deficient; AAV only replicates if the target cell is co-infected with a helper virus, such as an adenovirus (hence the term "adeno-associated virus").
- AAV is easy to engineer in the laboratory; the wild-type *rep* and *cap* genes can be removed and replaced with the gene cassette of interest, i.e., the FIX expression cassette, which is under the control of a nuclear-specific promoter. The ability to eliminate wild-type genes reduces the risk of mounting an immune response to the viral proteins.
- Recombinant AAV (rAAV) can transduce a variety of cell types and, in particular, mediate stable long-term transgene expression following a single administration of the vector into post-mitotic tissue such as the liver, muscle, retina, or brain. This expression is predominantly mediated by episomally retained copies which integrate rAAV at a very low frequency, similar with DNA vectors.
- The risk of insertional (vector-mediated) oncogenesis with AAV is substantially lower than what one might see with onco-retroviral vectors.
- There are multiple AAV serotypes which have distinct tissue tropism and immunobiology, with biological properties that broaden the scope for this vector system.

There have been previous clinical trials using AAV vectors for gene therapy of hemophilia B, pioneered by Kathy High, Mark Kay, and Glenn Pierce. The 2003 High study targeted muscle and showed that intramuscular delivery of AAV vectors in severe hemophilia B patients was not toxic but did not achieve FIX expression levels above 1% for longer than a couple of weeks in most patients.

The 2006 study by High et al. targeted the liver, which is the native site of FIX synthesis. Vector was delivered into the hepatic artery of seven patients with severe hemophilia B and shown to be a more efficient route for FIX expression. More importantly, transgenic proteins expressed in the liver were more likely to induce tolerance. The study showed that the low and intermediate doses were safe but did not result in any meaningful expression of FIX in the plasma. At the high-dose level, one subject had increased FIX expression of about 12% at two weeks after gene transfer, which held for another two weeks before declining back to baseline levels. The investigators hypothesized that AAV was broken down after entry into the liver cells and the capsids were then presented by hepatocytes to cytotoxic T cells believed to be a legacy of previous infection with AAV2.

These studies highlighted the need to find ways to circumvent the high level of AAV2 immunity prevalent in humans; a current clinical study led by Dr. High focuses on using immunosuppression at the time of vector administration. There is also a need for more potent AAV vectors so that therapeutic expression of FIX can be achieved using much lower doses of vector per bolus. The previous two studies showed that the risk of transaminitis is substantially lower when low levels of vector are administered; in fact, it was non-existent, suggesting that transaminitis seems to be related to the amount of protein load delivered into the patient.

The approach developed by the Haemophilia B Gene Transfer Study differs from previous clinical trials in three important aspects: enhancement of AAV potency, the use of AAV serotype 8 (AAV8), and peripheral vein vector delivery.

Enhancement of AAV potency to facilitate transduction with lower doses:

AAV is a single-stranded virus (ssAAV) that needs to be converted to a double-stranded form either via transcription of plus and minus strands or second-strand synthesis; currently, most of the AAV particles that we deliver are degraded wherever these particles end up. To overcome this limitation of the AAV viral biology, the investigators developed "self-complementary vectors" (scAAV) based on previous research by Judith Melki and David Russell, which created an expression cassette half the size of the wild-type AAV that was then preferentially packaged into a single AAV variant as plus and minus dimers. The expression cassette was further engineered to improve the efficiency of the packaging and facilitate the dimerization.

The theory was that after uncoating of the virus in target cells, the plus and minus strands come together to form a transcription, or the active double-stranded unit, which is then stably maintained. In mice, the scAAV mediate transgene expression was tenfold higher than with an equivalent ssAAV expression cassette. In non-human primates, administration of a dose of the scAAV that was substantially lower than ssAAV was shown to still result in higher levels of expression. Thus the engineering of the AAV genome allows mediation of higher levels of expression using lower amounts of vector particles.

Use of AAV serotype 8 to circumvent pre-existing immunity to AAV2:

The gene transfer strategy has focused on AAV8 pseudotyped vectors instead of AAV2 because it offers several advantages. There is substantially lower prevalence of pre-existing immunity to AAV8 among humans, as shown by the results of *in vitro* and *in vivo* transduction inhibition assays on both blood donors from the general population as well as hemophilia B patients in the U.K. A low seroprevalence rate allows researchers to exclude subjects with pre-existing immunity and thereby reduce the potential for cellular immune response to the capsid observed in the last clinical trial.

The team's study of seroprevalence of antibodies to AAV8 in the U.K. population showed that very few people had pre-existing immunity to AAV8 (in terms of the amount of antibody detectable in the plasma of blood donors and hemophilia B patients) and its data suggests that AAV8 is very poor at transducing and presenting antigen cells. This suggested that the likelihood of developing an immunological response to the AAV8 capsid would be substantially lower. They then looked at whether giving AAV8 to humans with pre-existing immunity to AAV2 would lead to cross-reactive immunity. Investigation in five non-human primates with levels of pre-existing antibody to AAV8 who were challenged with a different serotype, AAV5, showed that administration of AAV5 resulted in efficient gene transfer and FIX expression that was stably maintained for more than five years despite presence of high-titer antibodies. Thus there is no evidence of cross-reactive immunity to AAV serotypes, at least in a non-human primate model.

Peripheral vein administration vector:

Patients in various focus groups expressed the desire for vector delivery to be simplified in order for them to participate in clinical trials. Consequently the investigators looked at whether the same level of gene transfer could be achieved if the vector was delivered in the peripheral vein as opposed to more invasive delivery into the liver via mesenteric tissue or the hepatic artery. Infusion of the vector into the saphenous vein of three nonhuman primates was able to achieve the same level of gene transfer and FIX expression after a simple peripheral vein delivery of vector particles as compared to delivery of the vector either via mesenteric circulation or the hepatic artery. Quantitative polymerase chain reaction (qPCR) assay showed that biodistribution of this vector is not different regardless of whether the route of administration is in the peripheral vein or mesenteric vein. Thus the remarkable tropism of AAV8 for the liver facilitated the development of a simpler and potentially safer non-invasive method of vector delivery, at least in the patients with hemophilia B.

The primary objective of the clinical trial was to assess the safety of a simple bolus infusion of the self-complementary AAV vector pseudotyped with AAV8 capsid (at three dose levels) administered into the peripheral vein without any upfront immunosuppression. The secondary objective was to determine the dose of the scAAV required to achieve stable FIX expression above 3% of normal. The key criteria for eligibility were that patients be over the age of 18 with severe hemophilia B (FIX levels below 1% of normal) with no pre-existing immunity to AAV8.

In the knowledge that in the U.K. most patients have very good existing treatment, the investigators developed a robust informed consent process to be sure that patients understood that the experimental therapy could potentially provide no benefit as well as the theoretical risks (transaminitis, formation of cancer, inhibitor formation, etc.), which were graphically described in the patient information leaflet. An independent ombudsman formally assessed candidates on their understanding.

At the time that the trial was initiated, there wasn't a commercial outlet to make the AAV8, therefore the researchers developed the technology to produce high quantities of the vector and purify to levels required for use in humans. This took 18 months at a cost of about half a million pounds, with half the cost spent on the validation quality assurance/quality control analysis.

Three doses were assessed; starting with a low dose ($2x10^{11}$ qPCR-vg/kg) and in the absence of toxicity gradually evolving to intermediate dose ($6x10^{11}$ qPCR-vg/kg) and then high dose ($2x10^{12}$ qPCR-vg/kg). Six patients with severe hemophilia resulting from a missense, known or promoter mutation were recruited (age range of 27 to 64 years); two had no factor IX in their circulation. All of these patients were on prophylaxis once to three times weekly but despite prophylaxis, all reported bleeding episodes ranging from one to six episodes per year.

Dr. Nathwani summarized the findings to date:

- Six subjects to date have received the self-complementary vector scAAV2/8-LP1-hFIXco, with two subjects at each of three dose levels.
- Peripheral vein infusion of this vector was very well tolerated without any acute side effects.
- A dose-dependent increase in the vector load was observed in the blood, stools, and saliva. Vector genomes were present in the semen of some of the patients but none had any shedding into the urine. Importantly, all six patients had cleared the vector genome from their bodily fluids within three weeks of gene transfer.
- Liver function tests in four patients (two at the low dose and two at high dose level) showed that liver enzymes in all four patients remained at their baseline value but were substantially below the upper limit of normal, i.e., there was no preservation of liver enzymes in the first four patients recruited.
- There is evidence of stable FIX expression at 1-12% of normal in all six subjects for 5-16 months; four subjects have been able to stop prophylaxis and two have been able to extend the interval between prophylaxis.
- Improvement in quality of life is seen in all six subjects.
- The savings on prophylaxis so far for the U.K. government are in the order of £300,000, and will increase.
- Capsid-targeted cell-mediated immunity remains a concern; however, the study shows that starting subjects on a short course of steroids early on abrogates this immunological response and preserves FIX transgene expression.
- This is encouraging data for hemophilia B as well as other disorders affecting the liver.

Plans for the future are recruitment of four to six more patients at the high dose in 2011-2012 to try to answer questions that are still unclear:

- Will all the patients treated at the high dose level suffer preservation of liver enzymes from vector-mediated transaminitis?
- If so, is our "expectant" use of steroids, i.e., starting low-dose steroids at the earliest sign of trouble, sufficient to prevent transaminitis and preserve FIX expression at the therapeutic level?

This is to be followed by a Phase II/III clinical trial in 2013-2015. The study, which initially recruited patients from the U.K. only, is now open to patients worldwide.

Dr. Nathwani concluded by praising the bravery of the patients: "These individuals permitted us to perform a proof of concept study in them with no expectation of benefit but in the full knowledge that there was potential for significant toxicity."

Discussion

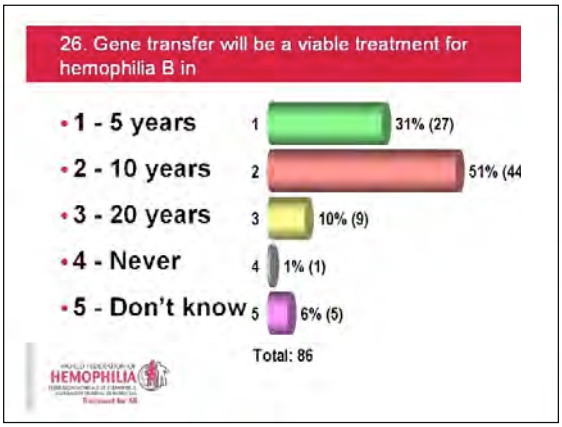
A participant asked whether the use of an osmotic mini-pump into the hepatic vein to provide slow continuous release of the vector over a prolonged period of time would increase expression in hepatocytes, rather than infusion of a large dose of vector at once into the bloodstream. Dr. Nathwani said this was tested in non-human primates. The investigators did not see an improvement in AAV8 expression, in terms of the level of gene transfer achieved on a molecular level or the FIX protein that is expressed, when delivered as a small low-dose infusion via mini-pump over a period of 72 hours compared to a bolus infusion; nor did they see an increase in the diversity of the hepatocytes transfused. While 72 hours may be a short period, prolonging it further raises issues about stability of the vector. Histology to show the presence of the protein in hepatocytes is difficult due to the homology between rhesus FIX and human FIX, therefore fluorescent *in situ* hybridization was done to show the presence of the genome.

A participant asked whether there is concern about the expression found in the semen. Dr. Nathwani replied that Kathy High's group has done studies which show that the genome is not present in sperm, it is present in the adventitial tissue cells that are present in the semen, so the view is that it is transient and not a concern.

A participant noted that vector production was initially done at St. Jude's Hospital. He asked if this is still the case or are there now other options, such as industrial partners, which would affect production costs. Technology for making vectors is improving on daily basis and the costs involved with making vectors are also going down, so in the future, the costs will be substantially lower, Dr. Nathwani said. This was a very expensive study because a lot of developmental work needed to be done; once that is all completed, the cost will go down. There are various industrial outlets that can now produce the vectors but production continues to done in-house.

A participant noted that in the severe combined immunodeficiency (SCID) gene therapy trial in children, 7 of the 10 patients developed malignancies and leukemias. How long will this study follow patients for oncogenic potential given that the risk is not zero? The regulators require that patients be followed for a minimum of 30 years but these patients will be followed through their lives, mainly by non-invasive methods such as annual ultrasound scan to carefully examine the liver and annual tumour marker studies, Dr. Nathwani said.

Participants were again polled on the predicted number of years until gene therapy becomes available for hemophilia B. This time, 51% voted that it would be available in 10 years; prior to the presentation, 40% voted that gene therapy would be available in 10 years. When polled again on gene therapy for hemophilia A, about 30% anticipated gene therapy becoming available in 10 years compared to about 24% prior to the talk. David Page noted that at the 2007 WFH Global Forum, about 25% of participants predicted that gene therapy would be available in 10 years, so the degree of optimism has doubled.



Solvent Detergent Cryoprecipitate – Clinical Experience Update

DR. MAGDY EL EKIABY, SHABRAWISHI HOSPITAL BLOOD TRANSFUSION CENTERS, CAIRO, EGYPT

The large majority of people with hemophilia around the world do not have access to safe treatment; in places where clotting factor concentrates are unavailable or unaffordable, patients rely on fresh blood components and face increased risk of blood-borne pathogens. The research project on solvent detergent cryoprecipitate was initiated in 2003 with the aim to offer these patients an option or alternative for access to safer treatment products. Research, development, and validation of the solvent detergent technology for viral inactivation have been achieved and preparation is underway to launch the device worldwide.

The solvent detergent pathogen inactivation medical device is a single-use sterile medical device that will enable blood centres to process mini-pools of plasma components (i.e., fresh plasma, fresh frozen plasma, cryoprecipitate-poor plasma, or cryoprecipitate) using solvent detergent for pathogen inactivation followed by sterile filtration. The technology is very simple and nothing needs to be added to the blood services. The medical equipment required are:

- shaker for controlled mixing of the solvent detergent agents;
- incubator for controlled mixing of solvent detergent and plasma or cryoprecipitate and controlled mixing of the reagent and blood component;
- injection pump for graded infusion of solvent detergent to the plasma or cryoprecipitate;
- syringe for solvent detergent extraction;
- medical device cascade of sterile PVC bags and electric sealer (for disconnection with each successive stage);
- integrated absorption filter for removal of any residual TnBP and 0.2 µm microbial filtration.

The pathogen inactivation procedure runs the plasma component through a cascade in separate stages in succession, with all the processes stacked in one simple medical device.

The medical device comes in a complete kit that includes the vials of Tri-n-butyl phosphate (TnBP) and triacyl glyceride, with the dose to be adjusted to the volume and validated; syringes including an oil syringe for solvent detergent removal; and the cascade of PVC sterile bags with integrated absorption filter for residual TnBP removal and 0.2 µm microbial filter. Separate kits are available for plasma and cryoprecipitate (SD Plasma Kit and SD Cryoprecipitate Kit). The devices are CE marked in Austria and have a free sales certificate from Swiss Medic, which produces the devices.

Solvent detergent viral inactivation of cryoprecipitate involves a number of steps:

- pooling of 30 units (400 +/- 20 mL) of dry cryoprecipitate, i.e., plasma has been removed from the cryoprecipitate;
- each cryoprecipitate unit is prepared from 200 mL of fresh frozen plasma or more and re-suspended aseptically in 8 mL of 5% glucose saline solution for infusion under aseptic conditions;
- solvent detergent treatment done in two stages;
- solvent detergent removal with one-point oil extraction step and one solvent detergent removal filtration step;
- 0.2 µm microfiltration;
- dispensing of treated pharmaceutical-grade cryoprecipitate into bags that are dose-labelled for FVIII and fibrinogen, with the option to add VWF or FXIII dose to the label.

Validation studies have been run in Cairo, Paris, and Lille. The viral validation study was conducted at the Texcell laboratory of the Pasteur Institute in Paris, according to CPMP/EMA guidelines and with "worst case" conditions (low range of less than 2%; 1.8% lower temperature of 29 degrees instead of 31 degrees; no transfer to second viral inactivation bag). Results showed more than 4 log reduction in two minutes; this can be assumed to be more than 6 log reduction because of the dilution effect when adding the spiking solutions of HBV, HCV and HIV virus models in cryoprecipitate, fresh frozen plasma, and cryoprecipitate-poor plasma.

The conclusions of the Pasteur viral validation study were that TnBP-Triton X-45 is very effective for viral inactivation and that the virus inactivation is very fast. The shape and design of the bag was determined appropriate to ensure good mixing between plasma and the solvent detergent.

The total inactivation process takes about 4-5 hours (about 70 hands-on minutes; 45 minutes to pool the 30 units of cryoprecipitate and 25 minutes for the rest of the procedure) thus there is very good recovery of all the cryoprecipitate proteins, with more than 100% recovery of FVIII coagulant activity and antigen; more than 85% recovery of fibrinogen; and from 90% to above 100% recovery of VWF antigens, ristocetin cofactor activity ratio, and collagen binding activity. Multimer analysis showed no change between the start cryoprecipitate and the five branches of the solvent detergent treated cryoprecipitate, and no anti-A or anti-B isoagglutinines in any of the validated pools.

The general qualities and characteristics of treated cryoprecipitate are:

- increased concentration of FVIII (7–11 IU/mL) compared to the normal cryoprecipitate and chance of improvement to 10–14 IU per mL;
- fibrinogen between 12–21 mg/mL;
- VWF components (RCo=11–16 IU/mL; CBA=11–18 IU/mL; Ag=15–18 IU/mL; multimers > 15 mers and > 10 mers = same as start cryoprecipitate);
- universal blood group ABO isoagglutinines (anti-A titer: 0; anti-B titer: 0);
- very low levels of residual TnBP and Triton X-45.

An animal safety study compared mice injected with solvent detergent treated plasma and treated cryoprecipitate to mice given normal plasma and cryoprecipitate as a control. The mice were followed for 14 days for weight gain, activity, and food consumption; there was no difference between the groups, proving that it could possibly be very safe.

The technology is now being tested and validated at different blood centres. The validation study results have been received from the Thai Red Cross and were almost identical to the results of the Cairo blood centre; other validation sites include Saudi Arabia and Tunisia. A small pharmacokinetic study of solvent detergent cryoprecipitate FVIII was conducted in late 2010 in 11 previously treated severe hemophilia A patients who were negative for inhibitors. The methodology involved:

- approval of Ministry of Health to import VIPS kits;
- institutional review board (IRB) approval;
- informed patient or family consent;
- FVIII wash out period of 7 – 10 days;
- infusion of solvent detergent cryoprecipitate FVIII at dose of 40 IU/kg +/- 6 IU;
- follow-up of solvent detergent cryoprecipitate FVIII recovery during 36 hours;
- recording of adverse events during 36 hours after infusion of solvent detergent cryoprecipitate.

Tolerance: Patients were admitted to the hospital for 36 hours and closely observed on their tolerance for solvent detergent cryoprecipitate during follow-up by regularly recording their basal pulse, basal blood pressure, and respiratory temperature. No adverse events (i.e., fever, rigors, hypotension, difficult breathing, shock, pulmonary edema) were observed and no prophylactic steroids or antihistamines were administered.

FVIII pharmacokinetics: The recovery was done at several time points; before infusion, 10 minutes after infusion, after 1 hour, then at 3, 6, 18, and 36 hours. There was recovery of about 70% after the infusion and a remaining factor level of about 11% after 36 hours. The half-life of the FVIII was about 14 hours; and the clearance rate was 2.6 mL $h^{-1}kg^{-1}$ (similar to plasma-derived and recombinant FVIII concentrates). The patients infused with this dose reported 8 to 22 days free from bleeding episodes after infusion; the patients were not on prophylaxis and usually had one bleed every 7 to 10 days, therefore there was prolongation of their bleeding free intervals.

Inhibitor development: There are now 15 previously treated hemophilia A patients with no inhibitors in the study; six have completed more than 15 exposure days with no inhibitor development and will be followed until 50 exposure days.

Surgical prophylaxis: The solvent detergent cryoprecipitate has been used for a number of surgical procedures (arthroscopic ankle arthrodesis, large umbilical hernia repair, knee arthroscopic synovial cauterization procedures, and circumcisions); the mean surgical prophylaxis dose was 35 IU/kg and the mean duration of surgical prophylaxis was five days. Successful hemostasis was achieved in all these procedures with neither bleeding episodes nor any adverse events.

The solvent detergent pathogen inactivation medical device for cryoprecipitate provides a number of enhanced safety features:

- viral inactivation of lipid enveloped viruses;
- small pool size limits the risk of lipid non-enveloped viruses (hepatitis A and parvovirus B19);
- removal of bacteria and parasites due to microbial filter (0.2 μm filter);
- removal of almost any residual cells or cell debris (0.2 μm filter);
- universal blood group solvent detergent cryoprecipitate.

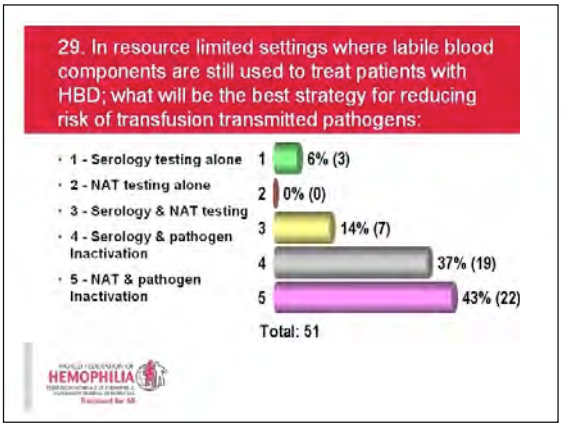
Discussion

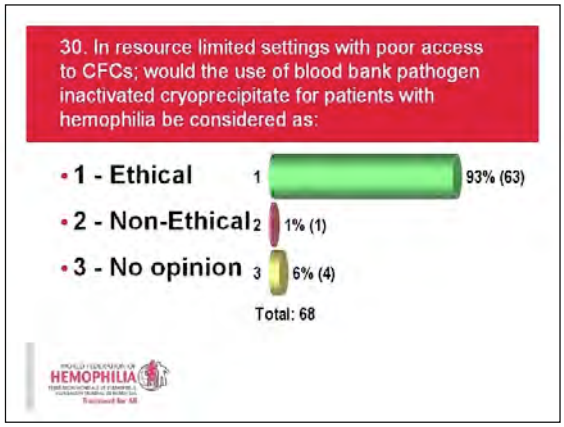
There were several remarks on the important benefits of the pathogen inactivation device, particularly for developing countries, and discussion on adverse reactions, validation of various blood components, volume variations for blood collection, and quality. A participant noted that the side effect profile of the pilot study looked at transfusion-related reactions. Does this involve blood-type specific or blood-type compatible cryoprecipitate and is the collection done in a blood-type compatible manner in terms of antibodies? Normal cryoprecipitate is usually type specific so it is indeed type specific, Dr. El Ekiaby said.

A participant asked whether the kit is also validated for recovered plasma or only for apheresis plasma. The validation study in Thailand involved recovered plasma; and the Cairo investigators also validated apheresis plasma, recovered plasma, fresh material, frozen thawed material and pooled cryoprecipitate material, Dr. El Ekiaby said.

The next question was whether this kit is correlated to a certain plasma volume given that the volume for whole blood collection varies a lot in developing countries (between 250-400 mL), and whether there is a limitation or interference with the collection volume of whole blood. Dr. El Ekiaby said that the validated volume for the time being is 400 mL +/-5% for the non-used space inside the bags for the viral inactivation and removal of the solvent and detergent. Companies are currently working on greater volume flexibility. Kit instructions should be precisely followed to ensure proper viral inactivation and proper removal of the solvent and detergent.

In the thawing of fresh frozen plasma, fibronectin is sometimes a problem. Were any problems encountered with this process? The study did not validate for fibronectin but there are ongoing studies with solvent-detergent plasma which show a safety edge similar to the cryoprecipitate, and no problems have been encountered so far, Dr. El Ekiaby said. The cost of the kits is a commercial decision belonging to the company but the SD Cryoprecipitate Kit is an extremely economical solution whereas the SD Plasma Kit is more expensive and more likely to be affordable to developed countries.





Manufacturers' Updates

The final presentations by various pharmaceutical companies showed some of the promising products under research and development or in the pipeline including more potent and longer-acting factors, some of which could possibly be on the market within several years.

Pioneering Designs for Recombinant Coagulation Factors

DR. DEBRA BENSEN-KENNEDY, CLINICAL RESEARCH AND DEVELOPMENT, CSL BEHRING

CSL Behring produces a broad range of coagulation factor concentrates and is committed to advancing treatment for rare bleeding disorders, Dr. Debra Bensen-Kennedy said. It is pursuing numerous research and development activities that aim to improve or enhance coagulation factors, including pioneering recombinant technology. The variety of avenues for improving coagulation factors are being explored: improved functional activity, reduced immunogenicity, alternative delivery, and half-life extension. Dr. Bensen-Kennedy described the pipeline products for the treatment of bleeding disorders, focusing on progress in half-life extension.

Potential advantages to be gained via factor concentrates with extended half-life include less frequent infusions, improved compliance, and improved quality of life; and the possibility to enable a realistic prophylaxis label for short-acting factors (e.g., FVIIa for patients with inhibitors). A key challenge in manufacturing is how to actually achieve half-life extension and how to weigh the different advantages and opportunities of various approaches. The goals are to identify the optimal half-life extension method, preserve biologic activity, and maintain a very strong safety profile in terms of immunogenicity and tolerability because otherwise the potential advantages of half-life extension might not outweigh the disadvantages of developing an inhibitor, she said.

CSL Behring's primary development program is focusing on half-life extension of recombinant activated factor VII (rFVIIa) and recombinant factor IX (rFIX):

- Recombinant factor VIIa is used to treat patients with FVIII or FIX inhibitors. It has a very short half-life of about 2.4 hours and several infusions can be required to control a bleed (two or more infusions for a joint bleed; every two to three hours in the surgical setting). The researchers hope to engineer an improved rFVIIa product and have set a goal for half-life extension such that one infusion would suffice per bleeding event; this is the minimum standard to move forward into clinical development.
- Recombinant factor IX is used to treat hemophilia B and has a long half-life of 20 hours that allows a prophylaxis schedule of two to three infusions per week. The goal is to develop an improved rFIX product with extended half-life such that one infusion per week would suffice to prevent and control bleeding; this is the minimum standard for clinical development.

The research has focused on albumin fusion technology. Albumin has a naturally long half-life of about 20 days. It is a carrier protein that is inherently inert to the immune system; humans all have abundant albumin in their blood. The structure and clearance mechanism are well understood. The proof of principle of albumin fusion with other complex proteins has been done to demonstrate the engineering capabilities, and it is now recognized that albumin fusion proteins can be expressed as a single recombinant entity.

The hypothesis is that fusion of recombinant factor and recombinant albumin into a single construct could extend factor half-life through the extended half-life of the albumin. The DNA construct that codes for both proteins is then expressed as a single recombinant molecule. DNA transfection into eukaryotic cells is followed by the selection process, protein secretion, and post-translational modifications; then fermentation, purification, and characterization of the molecule (i.e., does it meet the goals set for biological activity, pharmacokinetics, and efficacy in order to move into clinical development).

Albumin has been successfully fused with rFVIIa (rFVIIa-FP) and the optimal molecule and linker length have been determined. Efficacy modelling has demonstrated dose dependency and extended half-life has been demonstrated in pre-clinical models. The fusion process for rFIX-FP is somewhat different. The rFIX molecule needs to be activated; once the activation occurs, it breaks away from the albumin.

Pharmacokinetic studies in monkeys have examined kinetic and antigen activities at two dose levels, which were reproducible in different animals and demonstrated dose dependency. A threefold half-life extension has been observed. Pharmatoxicology trials have found no observed adverse effects of treatment following intravenous administration of rFIX-FP in rats, rabbits, and monkeys. Pharmacokinetic and pharmacodynamic studies in hemophilia B dogs have demonstrated reduced clotting time, threefold increased half-life, area under the curve, and mean residence time. Overall, both fused proteins appear to be very promising.

CSL Behring is also working on an improved factor VIII via development of a single-chain recombinant factor VIII product. The FVIII/VWF complex plays an important role in plasma physiological activity and clearance of FVIII and has been shown to influence the presentation of FVIII to the immune system. Therefore, one research goal is to improve binding with VWF.

One of the challenges of FVIII is its instability in the manufacturing environment due to possible dissociation of the FVIII heavy and light chains, which may affect stability and potency. Thus another research aim is to improve molecular stability. Researchers have successfully created a single chain DNA construct with an increased heavy/light chain association and enhanced molecular integrity with faster, more efficient binding to VWF. The molecule has a covalent linkage between the heavy and light chains that remains stable when reconstituted. Comparable efficacy was shown in tail tip bleeding models. The formal development phase is underway.

CSL Behring has also developed a highly active plasma-derived FVIII/VWF concentrate called Biostate® for the treatment of hemophilia A and von Willebrand disease. The product was launched in Australia in 2003 for hemophilia A and has been registered for VWD in Australia and New Zealand since 2008. It is currently in clinical trials moving towards centralized approval in the European Union and expected to be approved soon for use in other jurisdictions, she concluded.

Novel Treatment Options for Hemophilia

DR. PRASAD MATHEW, BAYER

Bayer has entered a new era in its approach to hemophilia treatment, all the while committed to "never losing sight of the human factor," said Dr. Prasad Mathew. The goal is to raise the bar for scientific innovation and research to address unmet clinical needs and improve the standard of care. "Our goal is for all people with hemophilia to confidently live the lives they choose," he said. He described Bayer's progress in developing improved recombinant FVIII, FIX, and FVIIa options.

Despite impressive advances in hemophilia therapies in recent decades, there continue to be significant unmet medical needs in hemophilia care, Dr. Mathew said. There is need for:

- reduced dosing frequency for prophylaxis;
- elimination of human and animal proteins in treatment products;
- reduction of inhibitor formation;
- heat stable formulations of products (at room temperature in the absence of refrigeration);
- development of non-invasive administrative routes;
- an eventual cure, possibly through gene or stem cell therapies.

To this end, Bayer is currently developing a novel longer-acting FVIII compound called BAY 94-9027. It contains a single B-domain-deleted site-specific pegylation, which has been demonstrated to retain full coagulation activity in pre-clinical models. Compared to rFVIII, it has shown a two- to threefold increased half-life in animal models, prolonged efficacy in bleeding models, and reduced immunogenicity in pre-clinical tests.

The researchers investigated whether pegylation blocks antigen uptake and demonstrated an 80% reduction in uptake/internalization of pegylated B-domain-deleted rFVIII (PEG-BDD rFVIII) in human dendritic cells; reduced activation of FVIII-specific T cells; and significantly reduced FVIII-specific antibody formation in hemophilia A mouse, rat, and rabbit *in vivo* models.

Given these promising results, Bayer initiated an open-label Phase I trial to evaluate the pharmacokinetics of BAY 94-9027 following single and multiple dose administration in previously treated patients with severe hemophilia A, and its safety profile over an eight-week period. The multicentre, non-randomized, non-blinded parallel-group study involves two cohorts receiving different dosages with multiple administrations over eight weeks. The sample size was set at 12-16 patients (6-8 patients per cohort). The first cohort was given a dose of 25 IU/kg twice weekly; 7 patients have completed the study so far. The second cohort was given a dose of 60 IU/kg once weekly; 7 patients have completed the study so far. This phase I study is ongoing.

Another product in clinical development is BAY 86-6150, a novel rFVIIa compound with better efficacy and longer half-life. It contains six amino acid changes resulting in increased binding to activated platelets, increased thrombin generation, reduced activity with tissue factor, increased half-life, and increased and prolonged efficacy in animal models. A Phase I study involving patients with hemophilia was completed and confirmed improved pharmacokinetics. Phase II/III trials will start in 2012.

The products in the Bayer pipeline have potential to increase convenience and support patient compliance with their treatment regimens. The extended half-life and efficacy of pegylated BDD-rFVIII (BAY 94-9027) would help optimize prophylaxis therapy and preserve efficacy to treat on-demand. The novel rFVIIa product (BAY 86-6150), through increased thrombin burst generation at reduced clearance, would enable effective bypass therapy. Other novel clotting factors and bypass compounds are also being researched and evaluated, he concluded.

Biogen Idec Hemophilia Research Update

DR. SNEJANA KRASSOVA, BIOGEN IDEC

Biogen Idec is making significant progress in advancing its clinical development of a new, fully recombinant and long-acting FVIII product (rFVIII-Fc) and FIX product (rFIX-Fc) based on proprietary monomeric Fc fusion technology, which uses the neonatal Fc receptor (FcRn) to transport factor proteins. Dr. Snejana Krassova described the biological mechanisms of the FcRn receptor which recycle proteins into circulation, results to date from animal studies, and Phase I/II clinical trials on rFVIII-Fc and rFIX-Fc, and the pivotal Phase III trials on safety, efficacy, and pharmacokinetics now underway.

The FcRn receptor is a protein with expression in endothelial cells and other tissues and has been demonstrated to be responsible for the long circulating half-life of Fc-containing proteins such as immunoglobulin G (IgG). The FcRn recycling pathway involves several main phases:

- Proteins are taken up by endothelial cells through pinocytosis.
- The Fc domain of IgG/Fc fusion proteins binds to intracellular FcRn, while non-binding proteins follow the lysosomal pathway and degrade in lysosome.
- The FcRn receptor recycles the Fc-containing proteins to the cell surface, avoiding lysosomal degradation, and they are released back into circulation.

Fc fusion technology has been used for over a decade in approved products for autoimmune disorders such as rheumatoid arthritis, plaque psoriasis, and idiopathic thrombocytopenic purpura. The traditional Fc fusion proteins are dimeric.

Biogen Idec is working to harness the FcRn recycling pathway to fuse and transport rFVIII and rFIX proteins, using proprietary monomer technology. rFVIII-Fc contains a single B-domain-deleted rFVIII molecule fused to the dimeric Fc region of human IgG1. rFIX-Fc contains a single FIX molecule fused to the same region.

Pre-clinical trials of rFVIII-Fc in hemophilic mouse, rat, and dog models showed a twofold increase in half-life compared to rFVIII. Trials of rFIX-Fc in mouse, rat, dog, and monkey models showed a three- to fourfold increase in half-life compared to rFIX. In FcRn knockout mice, there was no significant difference in half-life between the fusion proteins and standard proteins; however, when the FcRn was returned, the increased half-life also returned.

Tail vein transection bleeding models were used to evaluate the prophylactic efficacy of recombinant factor fusion proteins compared to recombinant factor:

- Hemophilia A mice were given either rFVIII-Fc 48 hours before transection or Advate® 24 hours before transection; the survival curve 24 hours after transection was similar in both groups. However, when the products were both infused 24 hours prior to transection, the survival curve of mice given rFVIII-Fc was 100% and only 60% for mice given Advate®.
- Hemophilia B mice were given either rFIX-Fc 72 hours before transection or BeneFIX® 24 hours before transection; survival curves were similar 24 hours after transection.

Both rFVIII-Fc and rFIX-Fc demonstrated acute activity and dose response, comparable to their market counterparts. Comparable acute activity and dose response indicate comparable effectiveness for resolving bleeds. The novel proteins also had prolonged pharmacokinetic and prophylactic properties.

Phase I and IIa clinical studies of rFVIII-Fc at two dose levels (25 and 65 IU/kg) have been completed in 16 previously treated patients with severe hemophilia A. Results indicate:

- 1.5 to 1.75 times increased half-life and mean residence time relative to Advate®, with comparable incremental recovery;
- no drug-related serious adverse events;
- most adverse events unrelated to the study drug;
- one case of dysgeusia (abnormal taste in the mouth);
- no inhibitor of anti-rFVIII-Fc antibody formation after single dose.

Phase I and IIa studies of rFIX-Fc at six dose levels (ranging from 1 to 100 IU/kg) in 14 previously treated patients with severe hemophilia B were also promising. Results indicate:

- threefold increased half-life and mean residence time relative to historical data for BeneFIX®, with 24% improved incremental recovery and 2.5 times reduced clearance;
- no drug-related serious adverse events;
- one case of dysgeusia and one case of headache which occurred the dosing day;
- no inhibitor or anti-rFIX-Fc antibody formation after single dose;
- no allergic reactions.

These results supported further development in Phase III studies. The A-LONG Phase III Pivotal Study is an open label, multicentre study of rFVIII-Fc in previously untreated severe hemophilia A patients. The primary goal is to assess safety, tolerability, and efficacy of rFVIII-Fc for on-demand treatment. Secondary objectives are to characterize the pharmacokinetic profile and range of doses and schedules required to adequately prevent bleeding in a prophylaxis regimen, maintain hemostasis in a surgical setting, or treat bleeding episodes in all treatment arms.

The B-LONG Phase III Pivotal Study is an open label, multicentre study of rFIX-Fc in previously untreated severe hemophilia B patients. The primary outcome measures are safety and tolerability including notable changes from baseline in physical examination, vital signs, laboratory values, and incidence of adverse events including inhibitor development; as well as number of breakthrough bleeding episodes. Secondary outcome measures are pharmacokinetic parameter estimates, on-demand and surgical efficacy, response to treatment, and product consumption. The study will assess different treatment regimens: low and high-dose prophylaxis, on-demand, and surgery. Both fusion protein products hold real promise to improve the lives of people with hemophilia by reducing the frequency of infusions while enhancing efficacy, Dr. Krassova concluded.

Manufacturing, Safety, and Efficacy of Recombinant FXIII

KIM JACOBSEN, PHD, NOVO NORDISK

Kim Jacobsen gave an overview of factor XIII (FXIII) deficiency and Novo Nordisk's clinical development of recombinant factor XIII (rFXIII), the manufacturing process, and the product's safety and efficacy. FXIII deficiency is a very rare autosomal recessive bleeding disorder that can occur in any ethnicity and equally affects males and females. It has a known prevalence of 1 in 2 million people. So far only 400 to 700 patients have been diagnosed worldwide, including about 200 cases found in the European Union, about 100 cases in the United States, and about 50 cases in Canada.

Individuals with FXIII deficiency are capable of initial clot formation to stop bleeding when it occurs. However, lack of FXIII activity leads to reduced resistance to fibrinolysis, which causes the unstable clot to dissolve. Bleeding tends to recur 12 to 48 hours after injury (called "delayed bleeding") and is severe in the majority of cases.

Characteristic bleeding sites are mostly similar to those in hemophilia; however, the intracranial site is much more significant for people with FXIII deficiency, who have a 30% risk of intracranial bleeding, either spontaneously or after mild trauma, particularly at a very young age. This risk is higher than in any other congenital bleeding disorder. Intracranial bleeding is the main cause of death and significant morbidity in people with FXIII deficiency.

Novo Nordisk has developed the first recombinant product for the treatment of FXIII deficiency; the currently available treatment products are all plasma-derived. Recombinant FXIII is identical to human FXIII-A_2. It is expressed in the intended form as an intracellular soluble zymogen protein (a highly purified protein that does not contain any other coagulation factors) in a yeast production strain, with no need for further processing or modifications. After fermentation, harvesting, and purification using four chromatography steps, rFXIII is standardized and stabilized and the final freeze-dried product is packaged in 2,500 IU vials. The normal circulating concentration of rFXIII is 50–150%, with a half-life of about 12 days.

The Phase III clinical study was designed for monthly dosing and trough level above 10% after four weeks to prevent bleeding. Enrolment was very challenging given the rarity of the disorder. There were 23 participating centres from 11 countries in Europe, the Mediterranean, and North America. The pivotal Phase III efficacy and safety trial (a prospective, open-label, single-arm trial) enrolled 41 patients with confirmed FXIII A-subunit deficiency; 33 patients completed the study. There were five patient withdrawals and three patients who discontinued treatment.

In terms of efficacy, the primary endpoint was to determine the rate of bleeding episodes requiring treatment with a FXIII-containing product, over a 52-week treatment period. rFXIII outcomes were compared to a historical control rate based on retrospective data from 2005, which showed a bleeding rate of 2.91 bleeds per year (range of 0 to 12 bleeds per year). The rFXIII study showed a highly significant reduction in bleeds; four patients had 5 bleeds in total, which is a mean bleeding rate of 0.138 per year (equivalent to about 1 bleed every seven years). All the bleeds occurred in children or teenagers and all were trauma-related. There were no severe bleeds and no intracranial or life-threatening bleeds. No patients were withdrawn due to lack of efficacy. Thus the trial results demonstrated that rFXIII is highly efficacious in preventing bleeds.

In terms of safety, a number of adverse events were of special interest: antibody formation, thromboembolic events, anaphylactic reaction, and lack of efficacy. Eight serious adverse events were reported; five were not likely related to the trial drug. There were three positive cases of non-neutralizing antibody formation, one deemed to be probably related to the trial drug while the other two were possibly related. These three patients were withdrawn from the trial but continued to be followed. There were also four cases of transient non-neutralizing antibodies, but these did not appear to be clinically relevant, as there were no rFXIII inhibitors, no changes in pharmacokinetics, and no clinically relevant immunogenicity to rFXIII. Overall, there were no deaths, no clinically relevant safety findings, and no clinically relevant changes in laboratory parameters.

The trial demonstrated that rFXIII provides a safe treatment option for patients with FXIII A-subunit deficiency. rFXIII appears to be a safe and efficacious treatment for people with congenital FXIII deficiencies and has been submitted to both the Food and Drug Administration in the U.S. and the European Medicines Agency for approval.

Session 6: Closing Panel

CHAIR: BRIAN O'MAHONY, CHIEF EXECUTIVE, IRISH HAEMOPHILIA SOCIETY

Perspectives on Risk

This session was full of debate and showed that vigilance of the prospective risks, given the lessons in the past, should be always in our minds, said Dr. Magdy El Ekiaby, session chair. Reflection on what happened in the past, what we have now, and what the future will bring should be always a continuous process. "The blood system's role is to respond to the public needs, which will change from time to time according to the progress of different situations," he said. "Science should be there to support or stop a particular change that is in favour of or against the particular interests of our communities."

The speakers focused on three elements of decision-making in blood safety. Dr. Judie Leach-Bennett of Canadian Blood Services discussed risk assessment by government bodies and authorities. Then Nathan Schaefer of Gay Men's Health Crisis (USA) and WFH President Mark W. Skinner addressed the blood donor deferral of men who have sex with men and requests for revisiting the deferral and the non-specialist category. Dr. Steven Kleinman of the Blood Systems Research Institute (USA) described the science of how to assess pathogen transmission risk in different scenarios and use different technologies to assess mathematical risks and residual risks to support decision-making. The session raised many issues but ultimately offered a mechanism on how to introduce a change when a change is needed.

Achieving a Safe and Affordable Supply

This session focused on health technology assessment in hemophilia. Albert Farrugia of the Plasma Protein Therapeutics Association presented the industry perspective, while Dr. Sanford Schwartz (USA) presented an academic perspective from the U.S. and discussed comparative effectiveness research. "There's no doubt that HTAs, comparative effectiveness research and economic evaluations of the benefits of hemophilia care are here to stay—they're with us, they're not going anywhere," said session chair Brian O'Mahony. "It may be necessary to change the goal posts somewhat and perhaps start comparing the incremental cost of hemophilia therapy to blood safety measures, and not to all the other health comparators out there."

It is important to follow how HTAs in hemophilia are carried out and the parameters being considered, and to try to persuade the HTA agencies to take a more holistic approach and look at the quality of life benefits not just for the person with hemophilia but for all of their family. An initiative in Europe will be looking at how HTAs will be carried out for a number of diseases including hemophilia. "We have to engage in these processes—if we want to influence the answers, we want to influence the questions they're asking," Mr. O'Mahony said. The results of the Swedish HTA will be coming out towards the end of that process, which will be very useful data when it's finished.

Update on Inhibitors

The inhibitors session was informative and generated many comments, said session chair Mike Soucie. Dr. Carol Kasper (USA) described the context and circumstances when the Bethesda test was developed and the trade-off in terms of sensitivity and specificity of the test that occurs with the assignment of any cut-off value for determining whether an inhibitor is present or not. Dr. Elena Santagostino then gave an update on the progress of a randomized controlled trial which is comparing the use of plasma-derived versus recombinant products in terms of inhibitor incidence. She also presented the early findings from of an ongoing multinational study looking at adverse events among people with hemophilia in Europe. Mike Soucie provided a brief update on work by the U.S. Centers for Disease Control and Prevention, particularly towards the development of a national surveillance system for inhibitors.

Dr. Corien Eckhardt (Netherlands) described an ongoing study of inhibitor risk in mild and moderate hemophilia patients which has collected a significant amount of data that will help identify the patients at risk for inhibitors, and hopefully lead to management guidelines that will minimize inhibitor risk for mild and moderate patients who in some respects can suffer some of the worst consequences.

Clinical Trial Design Issues

This session addressed work in progress regarding two issues, clinical trial design and potency assignment of clotting factor concentrates. Both these topics were trying to address the harmonization of the requirements in the European Union and the United States and the impact this would have not only in these regions but the rest of the world as well, said Dr. Alok Srivastava, session chair.

Dr. Donna DiMichele (USA) described the work to date of the clinical trial design project group of the International Society of Thrombosis and Haemostasis (ISTH) FVIII/FIX Scientific Subcommittee, and Dr. Srivastava presented a summary of the work to date by the potency assignment project group. Senior regulators from both the EU and the United States have participated in the project groups and allowed themselves in some ways to be reviewed in terms of the practices, which shows that they are sensitive to the concerns in the community with regard to clinical trial design and potency assignment issues. There is a lot of grey area but the discussion has started and could lead to a better situation, with all stakeholders having the same common goals of trying to get good products into the market as soon as possible and making sure that they are safe and effective. The documents eventually produced by the project groups could serve as useful guidelines for the regulators.

Dr. Jerry Powell then gave a provocative presentation which led to a lot of discussion and comments, which have been noted and will be considered and incorporated in the final documents from both these groups. Any additional comments are welcome and can be communicated to Donna DiMichele (U.S. National Institutes Health) and Anthony Hubbard (U.K. National Institute for Biological Standards and Control).

Novel Technologies

The hemophilia community is on the verge of having a whole new generation of therapies that represent the first truly significant change in hemophilia treatment in about 20 years, said session chair David Page. The optimism was reflected in the audience poll at the start of the session on gene transfer technology, in which a large number of the participants estimated gene therapy for hemophilia could be 5 to 10 years away. The research and studies are very promising.

There has also been great progress with the solvent detergent cryoprecipitate project led by Dr. Magdy El Ekiaby (Egypt), which will be very significant for people with factor VIII deficiency in developing countries who for the first time will have access to a safe and effective product.

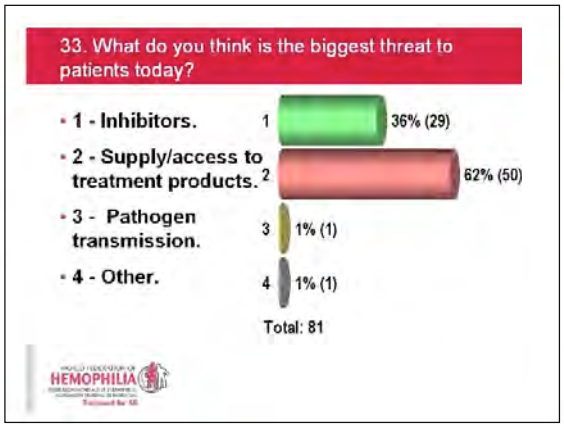
Finally, there were a number of presentations from the pharmaceutical industry on exciting products in the pipeline for both more potent and longer-acting factors, some of which are now in clinical trial phases and could possibly be on the market in two to three years.

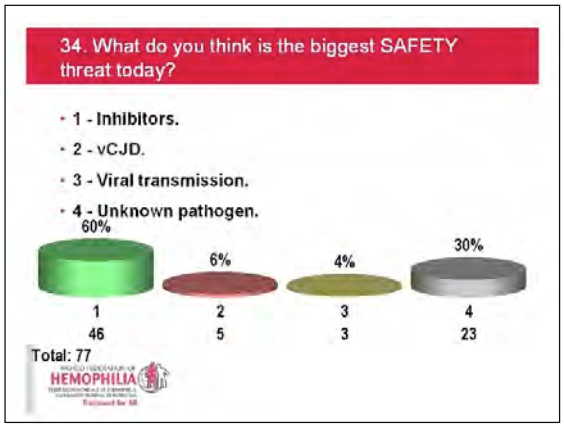
Closing Remarks

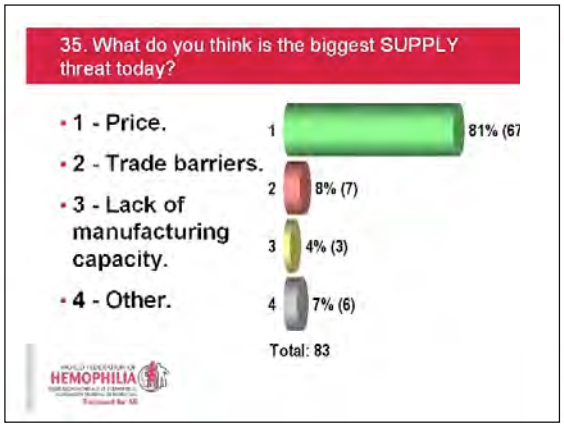
The 2011 WFH Global Forum focused on important topics in the treatment of hemophilia today, said WFH President Mark Skinner. The sessions covered a wide range of blood safety and supply issues—risk-based decision-making, health technology assessment, risk of inhibitors, pathogen inactivation, clinical trial design, harmonization of potency labelling, and novel technologies.

The Global Forum is useful within the WFH, which integrates the information and knowledge gained into its programs and activities going forward. He urged participants to fill out the evaluation forms to provide guidance and feedback to improve the meeting moving forward. In closing, Mr. Skinner thanked everyone for their attendance and participation, and WFH staff for their hard work organizing the meeting.

A final audience poll was taken using the original three questions posed at the start of the Global Forum on threats to patients, safety and supply to assess whether views had changed.







Glossary of Terms

Activated partial thromboplastin time (APTT): A test that measures clotting ability by measurement of the intrinsic pathway of the clotting system. Taken in conjunction with a normal prothrombin time, prolonged APTT is the most useful screening test for detecting deficiencies of factors VIII, IX, XI, and XII.

Adeno-associated viral vector (AAV): A non-pathogenic single-stranded DNA-based parvovirus that is endemic in humans.

Adverse event: An incident resulting in harm to a person receiving medical care.

Albumin: A protein found in human plasma that is used as a stabilizer in factor VIII and factor IX products including recombinant factor concentrates.

Antibodies: Proteins made by the body's immune system to fight off substances it perceives as foreign. Antibodies that occur in people with hemophilia are called inhibitors.

Bethesda assay: A laboratory test to detect the presence of FVIII or FIX inhibitors in patient plasma, which might be suspected from a reduced half-life and recovery of factor.

Biosimilars: Regulatory-approved versions of innovator biopharmaceutical products made by a different sponsor following patent and exclusivity expiry on the innovator product. Also called "follow-on biologics" or "generic biologics."

Biologics: Products of genomic and proteomic sciences are usually recombinant therapies capable of treating a range of diseases from hemophilia to rare cancers, at costs to patients and insurers that generally greatly exceed those of standard small molecule drugs. Biologics constitute a large and growing percentage of products being developed and marketed for orphan and common diseases. See also "biosimilars" and "generic biologics."

Bleeding disorders: Diseases in which the blood does not clot as quickly or as effectively as normal. Untreated, these diseases usually result in prolonged bleeding. These disorders include hemophilia A, hemophilia B, von Willebrand disease, platelet function disorders, and a variety of other rarer factor deficiencies.

Bolus: Infusion procedure in which a concentrated dose of a therapeutic product is given over a short period of time.

Bypassing agent: A special clotting factor used in patients with antibodies (inhibitors) to their usual factor, to overcome the blockage or cessation in the clotting system.

Centers for Disease Control and Prevention (CDC): The public health agency of the United States, responsible for health promotion, prevention of disease, injury and disability, and preparedness for new health threats.

Clotting factor concentrate (CFC): Fractionated, freeze-dried preparations of individual clotting factors or groups of factors derived from donated blood.

Characterization: Analytical measurements which allow detailed understanding of the composition and other attributes of a product.

Chromogenic assay: An assay based on the same principle as the two-stage clotting assay which focuses on the part of the coagulation cascade where FVIII acts; the endpoint is the formation of activated factor X. It is considered by some to be more accurate than the clotting assays, but it is less widely available in clinical laboratories. Currently, most European manufacturers uses the chromogenic method to label their products, whereas most. U.S. factor concentrates are labelled by the one-stage assay.

Clotting assay: An assay of FVIII:C, FIX, FXI, or FXII that can be done in one or two stages. The **one-stage FVIII assay** compares the ability of dilutions of standard and test plasma to correct the APTT of plasma that is known to be totally deficient in FVIII but containing all other factors required for normal clotting. For factors IX, XI, and XII, the assay substitutes the relevant deficient plasma for FVIII-deficient plasma, and after selection of the appropriate reference plasma. It is the least expensive and most widely used factor assay used in clinical labs. In the **two-stage FVIII:C assay**, adsorption of plasma by aluminium hydroxide removes activated factors and vitamin K–dependent factors; this removes prothrombin from the initial incubation mixture. The dilutions of adsorbed standard and test plasma are incubated with the combined reagent in the first stage, then a source of prothrombin and fibrinogen from pooled normal plasma is added in the second stage, which allows a clot to form; the resulting clotting time is dependent on the initial amount of factor VIII:C.

Clotting factor: Any of the factors in blood plasma that work together to form a clot to help stop bleeding.

Co-efficient of variation (CV): A normalized measure of dispersion of a probability distribution.

Comparative effectiveness research (CER): The direct comparison of existing healthcare interventions to determine which work best for which patients and which pose the greatest benefits and risks, usually with the goal to guide evidence-based decision-making. Also called "relative effectiveness" research.

Cost-effectiveness: Description applied to an intervention (treatment, diagnostic test, etc.) for which the costs are considered to be justified by the benefits provided.

Cost-effectiveness analysis: An economic evaluation in which the results are expressed as a ratio of cost per unit of health outcome, the latter normally being expressed in "natural units"; e.g., average blood pressure, change in blood pressure, symptom-free days, bleeds avoided.

Cost-utility analysis: A form of cost-effectiveness analysis in which the results are expressed in terms of cost per QALY gained.

Cryoprecipitate: A fraction of human blood prepared from fresh plasma. Cryoprecipitate is rich in factor VIII, von Willebrand factor and fibrinogen (factor I). It does not contain factor IX.

Donor screening: Individual donations of blood are screened to ensure that blood-borne viruses do not enter the plasma pool. Screening is currently available for HBV, HCV, and HIV.

Donor selection: Procedures designed to identify and exclude donors at risk of being infected with viruses that can be transmitted by blood transfusion.

Effectiveness: The effect of a treatment as measured in the usual clinical environment.

Efficacy: The effect of treatment as measured in the controlled environment of a clinical trial.

Efficiency: The allocation of resources in such a way as to maximize the total amount of benefit.

End user: The ultimate consumer of a product, especially the one for whom the product has been designed, manufactured, or procured.

Enveloped/lipid enveloped viruses: The common transfusion transmitted viruses HIV, HCV, and HBV, which are all characterized by a lipid viral envelope and are highly infectious.

European Medicines Agency (EMA): A decentralized agency of the European Union, responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU.

Evidence-based data: Information gained from scientific investigation, including clinical trials and reviews of published studies.

F8 and F9 genes: Factor VIII and factor IX genes.

Factor VIII (FVIII): A clotting factor manufactured in the liver. Deficiency or absence of factor VIII clotting activity results in hemophilia A.

Factor IX (FIX): A clotting factor manufactured in the liver. Deficiency or absence of factor IX clotting activity results in hemophilia B.

Factor concentrates: See "clotting factor concentrates."

Food and Drug Administration (FDA): The regulatory agency in the U.S. with core functions in medical products and tobacco, foods, operations, and global regulatory operations and policy.

Fractionation: The process of separating and processing human blood plasma into a range of products for therapeutic use.

Fresh frozen plasma (FFP): Human plasma separated from blood cells and platelets soon after donation and frozen at -30°C. FFP contains all the clotting factors, but at very low concentration to volume. FFP can be freeze-dried (fresh dry plasma) obviating the need for freezer storage.

Generic biologics: Less expensive generic versions of biologics. See also "biosimilars."

Half-life: The time is takes for infused factor to lose half of its potency. Factor VIII has a half-life of 8 to 12 hours. After the first infusion, the half-life of factor IX increases to 18 to 24 hours for subsequent infusions.

Health economics: The application of the theories, tools, and concepts of economics to thealth and health care. Health economics is concerned with the allocation of scarce resources, and health.

Health technology assessment (HTA): A review of the evidence (usually a systematic review) on the impact of a healthcare intervention (or "technology"), often including economic evaluation evidence.

Hepatitis: An inflammation of the liver caused by injury or viral infection through blood product transfusion. The most common strains of the virus are hepatitis A, B, and C. The introduction of screening and viral inactivation methods has eliminated transmission of hepatitis B and C through blood products. Hepatitis A (HAV) has been resistant to current viral inactivation methods, however, a vaccine is available. It is recommended that people with hemophilia get vaccines against both hepatitis A and B.

Hepatitis B (HBV): A virus that causes inflammation of the liver; HBV can be transmitted by needle sticks, body piercing and tattooing using non-sterilized instruments, dialysis, sexual contact, childbirth, and, in very rare cases, by fresh blood components.

Hepatitis C (HCV): A virus that causes inflammation of the liver; HCV is usually spread through contaminated blood transfusions, hemodialysis, and needle sticks.

Hemophilia A: An inherited bleeding disorder resulting from factor VIII deficiency.

Hemophilia B: An inherited bleeding disorder resulting from factor IX deficiency.

Hemophilia treatment centre (HTC): A specialized medical centre that provides diagnosis, treatment, and care for people with hemophilia and other inherited bleeding disorders.

Human immunodeficiency virus (HIV): A retrovirus that causes Acquired Immunodeficiency Syndrome (AIDS).

Immune tolerance induction therapy The infusion of high doses of the missing clotting factor concentrate 3-7 times per week for very long periods of time—months or years. The objective of the therapy is to allow the body's defenses to become accustomed to the foreign factor and to stop making antibodies against it, so that normal doses will be effective in stopping bleeding.

Immunogenicity: The ability of a particular substance, such as an antigen, to provoke an immune response.

Immunoglobulin G (IgG): Antibody molecules. IgG is composed of four peptide chains; two heavy chains γ and two light chains. Each IgG has two antigen binding sites.

Incidence: The number of new cases of a disease in a population over a period of time.

Incremental cost-effectiveness ratio (ICER): The difference in costs between one intervention and an alternative, divided by the difference in outcomes. An ICER is the technical term for measuring a unit of outcome, for example, a QALY or bleeds avoided.

Inhibitors: Antibodies to infused factor VIII or factor IX produced by the immune system that attack and destroy the factor VIII or IX proteins in factor concentrates, making treatment ineffective. A **high titer inhibitor** measures more than 5 Bethesda Units. High titer inhibitors are stronger and destroy the factor concentrate more quickly. A **low titer inhibitor** measures at less than 5 Bethesda Units.

International Society of Thrombosis and Haemostasis (ISTH): An international non-profit organization for the advancement of understanding, prevention, diagnosis and treatment of thrombotic and bleeding disorders.

International Unit (IU): A standardized measurement of the amount of factor VIII or factor IX contained in a vial. Usually marked on vials as 250 IU, 500 IU, or 1,000 IU.

Marketing authorization: The formal permit from a regulatory authority allowing a manufacturer to market a product following that authority's scrutiny.

Mild hemophilia: Condition resulting from a level of factor VIII or factor IX clotting activity between 6 to 24% of normal activity in the bloodstream.

Mini-pools: Plasma samples pooled from several donations, and then tested for viral markers.

Moderate hemophilia: Condition resulting from a level of factor VIII or factor IX clotting activity between 1-5% of normal activity in the bloodstream.

Modified Nijmegen-Bethesda test: Modified Bethesda test for inhibitors for improved specificity and reliability.

Log reduction: A measurement of the effectiveness for a particular virus and bacterial removal process. One log reduction may reduce the number of infectious units, such as viruses and bacteria, by 90%, two log reductions by 99%, three by 99.9% and so on.

Nanofiltration: A method of removing certain viruses and impurities from a protein solution. The solution passes through a small pore filter that removes viruses but allows therapeutic proteins to pass through.

Neoantigenicity: New epitopes which can be produced by altering the structure of the protein and are called neoantigenic determinants because they give rise to new antigenic determinants and require separate, specific antibodies for recognition.

Non-enveloped /non-lipid enveloped viruses: Pathogenic viruses (for example, HAV or parvovirus B19) which lack a lipid envelope and therefore are not susceptible to viral inactivation techniques such as solvent-detergent treatment.

Nucleic acid testing (NAT): Testing for viral nucleic acid, used to detect viruses. NAT allows the detection of viruses before the development of immunological markers of infection. NAT can be performed on both individual blood donations and mini-pool donations.

On-demand therapy: An infusion of factor concentrate as soon as the person with hemophilia is aware of a bleed. The goal is to promptly stop the bleed.

Outcome: The impact or result of a test or treatment on the health of a patient.

Parvovirus B19: A virus carried by a large percentage of the human population that is normally harmless. See "non-enveloped/non-lipid enveloped viruses."

Pharmacokinetics: The action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

Plasma: Part of the blood that contains fibrin and clotting factors.

Plasma-derived products: Factor concentrates that contain factor VIII or IX that have been fractionated from human blood.

Plasmapheresis: A method of collecting plasma from donors whereby only the plasma is removed; this allows a donor to donate a larger volume of plasma at a time and donate more frequently than is possible when donating whole blood.

Plasma Protein Therapeutics Association (PPTA): The organization for commercial manufacturers of clotting factor concentrates.

Potency: The biological activity measured in laboratory that is best related to a product's actual therapeutic effect.

Potency assignment/labelling: All therapeutic concentrates are labelled using International Units (IUs), assigned by clotting APTT assay or chromogenic assay. The European Medicines Agency (requires labelling by the chromogenic method and the U.S. Food and Drug Administration requires labelling by the clotting method.

Prevalence: The total number of cases of a disease in a given population at a specific time.

Product specification: The properties of a product which can be measured in laboratory, allowing a manufacturer to assess and demonstrate fitness of purpose.

Prophylaxis: The intravenous injection of blood-derived or recombinant product in order to prevent bleeding.

Purity: The proportion of the desired ingredient (e.g., FVIII in concentrates), relative to other ingredients present.

qPCR assay: Quantitative polymerase chain reaction assay; a laboratory technique used to amplify and simultaneously quantify a targeted DNA molecule.

Quality of life (QOL): A person's subjective well-being, often encompassing physical, psychological, and social dimensions.

Quality-adjusted life year (QALY): A measure of benefit of health care combining the impact on both expected length of life and quality of life.

Quality assurance system: A mechanism for achieving, sustaining, and improving product quality.

Quarantine: The holding back of a blood product or other drug for a short period of time because of a possible problem with its quality.

Recombinant factor concentrate: A preparation of factor proteins manufactured using recombinant (genetic) technology and, therefore, not derived from human blood.

Recovered plasma: Plasma collected as a by-product of donated whole blood. Recovered plasma is generally procured from unpaid donors.

Recovery: The amount of clotting factor concentrate a person's body can actually use to stop bleeding compared to the amount infused.

Registry: A database or record of identified people with hemophilia or inherited bleeding disorders. A registry includes information on personal details, diagnosis, treatment, and complications.

Resources: Inputs into the production of health care or goods and services in the economy generally. These would include staff time, hospitals, drugs, equipment, etc., and patients' time undergoing treatment.

Seronegative: Blood that has tested negative for a particular infection, such as HBV or HIV, i.e., results show the person does not have HBV or HIV.

Seropositive: Blood that has tested positive for a particular infection, such as HBV or HIV, i.e., results show the person has HBV or HIV.

Severe hemophilia: Condition resulting from a level of factor VIII or factor IX clotting activity of less than 1 % in the bloodstream.

Solvent detergent cryoprecipitate technology: A single-use solvent detergent pathogen inactivation medical device that enables blood centres to process mini-pools of plasma components without any additions to the blood services.

Source plasma: Plasma collected from donors through a process known as plasmapheresis, which removes only the donor's plasma. The majority of this plasma is obtained from paid donors.

Titer: The strength of a solution as determined by titration. In medicine it is used to describe the amount of antibodies present in a known volume of serum; in hemophilia, this is referred to as "inhibitor titer." See also "inhibitors."

Tolerized: A patient is "tolerized" when the inhibitor to factor VIII or IX has disappeared and does not re-appear with further treatment of factor VIII or IX.

Transaminitis: Elevated transaminases, commonly the transaminases alanine transaminase (ALT) and aspartate transaminase (AST), whixh may be an indicator of liver damage.

Validation: The action of proving that any material, process, procedure, activity, system, or equipment used in manufacture or control can and will reliably achieve the desired and intended results.

variant Creutzfeldt Jakob Disease (vCJD): A fatal brain disease thought be the result of eating contaminated beef products. vCJD is the human form of bovine spongiform encephalopathy (BSE) and is believed to be caused by an infection with a mutant protein called a prion.

Viral inactivation: The process of making certain viruses non-infectious, without necessarily removing them from the product.

von Willebrand disease (VWD): Inherited blood disorder caused by a defect in the VWF/factor VIII molecule, which results in prolonged bleeding and poor coagulation. VWD can affect both males and females.

von Willebrand factor (VWF): A blood glycoprotein that is involved in hemostasis; it is deficient or defective in VWD and is involved in a large number of other diseases.

World Health Organization (WHO): The directing and coordinating authority for health within the United Nations system.

Window period: The period between when a blood donor is infected with a virus or disease-causing agent and when infection can be detected by an immunological marker. During this period the donor is infectious but the infection is undetectable. The window period can be shortened with nucleic acid testing.

List of Acronyms

AAV: Adeno-associated viral vector
ACBSA: U.S. Advisory Committee on Blood Safety and Availability
APTT: Activated partial thromboplastin time
BU: Bethesda unit
CDC: U.S. Centers for Disease Control and Prevention
cDNA: Complementary DNA
CER: Comparative effectiveness research
CFC: Clotting factor concentrate
CHAMP: CDC Hemophilia A Mutation Project
DDAVP: Desmopressin
EMA: European Medicines Agency
FDA: United States Food and Drug Administration
FVIII: Factor VIII
FIX: Factor IX
FcRn: neonatal Fc receptor
HAMSTeRs: Haemophilia A Mutation, Structure, Test and Resource Site
HBV: Hepatitis B virus
HBsAG: HBV surface antigen
HCV: Hepatitis C virus
HPV: Human papilloma virus
HGVS: Human Genome Variation Society
ID NAT: Individual donation nucleic acid testing
IgG: Immunoglobulin G
ICER: Incremental cost effectiveness ratio
IPFA: International Plasma Fractionation Association
IRB: Institutional review board
ISBT: International Society of Blood Transfusion
ISTH: International Society of Thrombosis and Haemostasis
MSM: Men who have sex with men
NAT: Nucleic acid testing
NIH: United States National Institutes for Health
PEG-BDD rFVIII: pegylated B-domain deleted rFVIII
PTP: Previously treated patient
PUP: Previously untreated patient
QALY: Quality-adjusted life year
QOL: Quality of life
qPCR: Quantitative polymerase chain reaction
rAAV: Recombinant adeno-associated vector
rFVIIa: Recombinant activated factor VII
rFVIIa-FP: Recombinant FVIIa Fc fusion proteins fused with albumin
rFVII: Recombinant FVIII
rFVIII-Fc: Recombinant FVIII Fc fusion proteins
rFIX: Recombinant FIX
rFIX-Fc: Recombinant FIX Fc fusion proteins
rFIX-FP: Recombinant FVIIa Fc fusion proteins
scAAV: Self-complementary adeno-associated vector
ssAAV: Single-stranded adeno-associated vector
TRIM: Treatment of Inhibitors in Mild/Moderate Hemophilia Study
UDC: Universal Data Collection
vCJD: variant Creutzfeldt Jakob Disease
VWD: von Willebrand disease
VWF: von Willebrand factor
WHO: World Health Organization
WP: Window period

The World Federation of Hemophilia gratefully acknowledges
the sponsors of the 2011 WFH Global Forum:

Héma-Québec

Ministère des Relations Internationales du Québec
(Quebec Ministry of International Relations)

Ministère de la Santé et des Services Sociaux Québec
(Quebec Ministry of Health and Social Services)

The Proceedings of the World Federation of Hemophilia's Seventh Global Forum
on the Safety and Supply of Treatment for Bleeding Disorders

Published by the World Federation of Hemophilia

Additional copies are available from the WFH at:
World Federation of Hemophilia
1425 René Lévesque Boulevard West, Suite 1010
Montreal, Quebec H3G 1T7 CANADA
Tel.: (514) 875-7944 | Fax: (514) 875-8916
E-mail: wfh@wfh.org | Internet: www.wfh.org