

The World Federation of Hemophilia's Sixth Global Forum

on the Safety and Supply of
Treatment Products for
Bleeding Disorders

Proceedings

September 24 & 25, 2009
Montreal, Canada
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WFH Sixth Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders

Making the Case for Clotting Factor Concentrates

**September 24-25, 2009
Montreal, Quebec**

Proceedings

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Executive summary

Introduction

The Sixth WFH Global Forum, titled **Making the Case for Clotting Factor Concentrates**, was held in Montreal, Quebec, September 24-25, 2009. This global forum drew its highest attendance yet: 176 participants from more than 30 countries, including patients, medical professionals, industry representatives, and health and regulatory officials. Clotting factor concentrates are crucial to hemophilia treatment. The forum focused on trends in supply and usage worldwide, different prophylaxis regimens and outcomes, research on inhibitors, and progress in the development of novel therapies for hemophilia and other inherited bleeding disorders.

Key sessions examined several current and emerging issues that could potentially affect hemophilia care and supply and availability of treatment products: health technology assessments of hemophilia in Sweden and the United Kingdom; proposed healthcare legislation in the United States on comparative effectiveness research and on regulatory approval of generic biologics; and variant Creutzfeldt Jakob disease transmission and screening, in light of the first reported case of transmission of infection via plasma-derived products. Throughout the forum, participants were polled to assess perceptions within the bleeding disorders community. The results from the first poll showed that inhibitors are now perceived as the biggest safety threat to patients, surpassing pathogen transmission, while price is seen as the biggest threat to product supply.

Global Factor Usage and Trends in Supply and Demand

Dr. Jeffrey Stonebraker presented findings from recent studies on worldwide factor use and hemophilia A prevalence. The studies examined data from 104 countries from 1996 to 2006. The results are summarized as follows:

- The average annual per capita factor VIII use varies by national economies.
- In the majority of countries, factor VIII use is less than 1 International Unit (IU) per capita.
- Per capita factor VIII use in countries increased steadily over an 11-year period.
- Some countries have unusually high factor VIII use per person with hemophilia A compared to other countries within the same economic classification.
- There was significant variability in the reported hemophilia A prevalence across the different economic classifications.

Patrick Robert discussed how potential changes to the supply of coagulation factors could occur should there be approval of intravenous immune globulins (IVIG) for the treatment of Alzheimer's disease. This approval could occur by 2012, and the demand for IVIG for Alzheimer's disease would be in full speed by 2015, leading to greater amounts of plasma being processed, and increased production of byproducts of IVIG production such as clotting factor concentrates.

Prophylaxis Models

Dr. Kathelijn Fischer gave an overview of the evolution of the prophylactic regimen developed at the Van Creveld hemophilia centre. The Van Creveld prophylaxis regimen for severe hemophilia was established in 1969. Initially, treatment was based on bleeding patterns instead of target trough levels. Currently, prophylaxis is started much earlier and the prophylactic dose has doubled, resulting in a decreased average number of joint bleeds per year and improved Pettersson scores. These outcomes suggest that more intensive treatment yields better results. In addition, patients with severe hemophilia and no inhibitors who permanently stopped prophylaxis had slightly more joint bleeds per year than patients on continuous prophylaxis.

Dr. Victor Blanchette presented an overview of the Canadian Dose-Escalation Primary Prophylaxis Study and compared some of its findings to the U.S. Joint Outcome Study. The Canadian study is following children with severe hemophilia A. The study protocol involves dose escalation according to bleeding pattern. MRI of patients with a history of joint bleeds detected early osteochondral changes in 50 per cent of children; however, osteochondral changes were detected by MRI in only 7 per cent of the patients in the U.S. study. Future and longer-term studies are needed to examine the outcome of different primary prophylaxis regimens.

Cost and limited availability of factor concentrates are the most critical challenges in hemophilia care in developing countries. The Musculoskeletal Function in Hemophilia in the Developing World Study (MUSFIH) documented musculoskeletal outcomes in 234 children with severe hemophilia receiving varying levels of factor replacement therapy. Though on-demand treatment successfully controls bleeds, reduces pain, and increases survival, it does not prevent the development of joint damage by 20 years of age. Dr. Alok Srivastava estimated that it would be possible for countries with as little as 1 IU per capita available to provide low-dose prophylaxis to children with severe hemophilia A, leading to significant reductions in hemarthrosis.

Economics and Outcome Assessments

Brian O'Mahony noted that over the past 20 years, many developed countries have been able to provide an ample supply of factor concentrates for hemophilia treatment, with prophylaxis available for children and many adults, and no restrictions on clinicians. However, with the current global economic recession, this environment is changing and hemophilia as a high-cost condition will likely be increasingly examined by governments and their health economists.

Dr. Michael Lauer stressed the importance of Comparative Effectiveness Research (CER), as a component of evidence-based medicine. The U.S. stimulus bill introduced in February 2009 dedicated \$1.1 billion for CER with the goal of maximizing effectiveness of healthcare delivery. CER can help address the high cost of health care by making valid comparisons of different treatment options or strategies. This involves studying data from actual patients to measure treatment outcomes, and may be a way to address major gaps in evidence, and provide research that is directly informative as it is based on practice and policy.

Adam Hutchings noted that across European healthcare systems, every disease area with the exception of hemophilia has been subject to cost-constraint mechanisms in recent years. This is due to the fact that hemophilia is a rare, congenital bleeding disorder, and can be a very severe condition. Due to the global economic recession the cost-effectiveness of prophylaxis compared to on-demand therapy could come under payer scrutiny, and payers may cap hemophilia budgets. Patient organizations and clinicians will thus need

to educate healthcare decision-makers and payers about hemophilia and the important benefits that patients receive from investments in hemophilia care. Having evidence-based data on patient benefits will be crucial in this regard.

A Streamlined Regulatory Pathway for Biologics

This session, chaired by WFH president Mark W. Skinner, addressed the development of biosimilars. It is important to determine whether these medicines would be safe, appropriate and feasible alternatives to biologics that are currently in use, particularly due to proposed legislation on a streamlined approval process for biologics as part of healthcare reform in the U.S. According to poll results, the majority of the participants felt that biosimilars would be potentially good for the bleeding disorders community.

Diane Edquist Dorman gave an overview of the National Organization for Rare Disorders (NORD), which is dedicated to the identification, treatment, and cure of rare disorders. The high cost of orphan drug products is adversely affecting patients with rare diseases, as insurers are increasingly targeting orphan drugs and increasing the costs of co-payments or refusing to cover treatments. Industry must have incentives to develop new products as well as lower orphan drug costs so that patients and doctors have access to new treatments for rare and orphan diseases.

Jay Greissing of the Plasma Protein Therapeutics Association (PPTA) outlined some of the issues and challenges related to an abbreviated pathway for the approval of biosimilars. The proposed legislation to create an abbreviated approval pathway for biologics requires that manufacturers demonstrate that their biosimilar product has no clinically meaningful differences from the licensed biologic in terms of safety, purity, and potency. A critical question for hemophilia patients is whether the potential risks associated with an abbreviated process for biologics will be worth it in the long term. With biosimilar products, there are unknowns about the risk of adverse events including inhibitor development. Given that treatment of inhibitors is very expensive, the risks and unknowns of biosimilars could offset the potential cost savings hoped for from biosimilars.

Johanna Gray discussed two proposed legislative bills put forward to the U.S. Congress, which contain a provision to create a regulatory pathway for biosimilars. The U.S. National Hemophilia Foundation (NHF) supports the creation of a regulatory pathway for biosimilars while also identifying the following principles as crucial to any biosimilars legislation: safety and efficacy, clinical trials, interchangeability, and the exclusivity period. The NHF recommends appropriate resources and increased funding be provided to the FDA so that it can ensure the safety and efficacy of biosimilars under the new mandate.

Inhibitors Studies

Inhibitor development is a serious complication in hemophilia as it can reduce treatment efficacy and greatly increase cost of patient care. Several studies are underway around the world to examine various aspects of inhibitors. However, 58 per cent of the audience polled was not involved in a national or international study of inhibitors.

Dr. Mike Makris gave an overview of the adverse event monitoring system in the U.K. and Europe. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) tracks adverse events in hemophilia patients in the U.K. The data on incidence of inhibitors in the U.K. shows a correlation between inhibitor development and disease severity; patients with severe hemophilia have an increased risk of inhibitor development. The European Hemophilia Safety Surveillance (EUHASS) project is a multinational, prospective surveillance project.

Dr. Elena Santagostino presented an overview of three initiatives (PedNet, RODIN, and SIPPET) to study inhibitor development in previously untreated patients (PUPs), since these patients have a higher risk of developing antibodies to factor concentrate. Dr. Deborah Brown described two laboratory studies that have been designed with the capacity to be harmonized with clinical and epidemiological studies; the Hemophilia Inhibitor Genetics Study (HIGS) and the Hemophilia Inhibitors PUP Study (HIPS).

Dr. Mike Soucie presented an overview of a Pilot Study of Surveillance for Inhibitors in the U.S. which provides more detailed information about inhibitors. The study will enroll patients of all ages with hemophilia A or B, and there will be ongoing data collection about exposure to treatment and complete gene sequencing, as well as annual inhibitor testing. According to poll results, 49 per cent of the audience felt that variable treatment and testing practices are the most significant barriers to successful data harmonization, underscoring the importance of this study.

Variant Creutzfeldt Jakob Disease: Transmission, Testing and Risk Assessments

David Page discussed the continuing concern about the possible risk of transmission of variant Creutzfeldt Jakob disease (vCJD) through blood products. A vCJD screening test able to detect prions in blood donations may become available in the near future; however, the prospect of vCJD testing has many implications for both blood donors and recipients of plasma products.

Albert Farrugia described some vCJD risk assessments conducted to date and their outcomes. A number of countries have performed vCJD risk assessments in the past decade. These risk assessments have produced varying estimates but they all agree on two important points – that plasma-derived factor VIII products have the highest possible relative risk and clearance during the production process is most critical to actually minimizing risk as much as possible.

Dr. George Adams gave an overview of the vCJD Blood Screening Assay developed by Amorfix Life Sciences. The European Commission's draft Common Technical Specifications for vCJD specify that an assay must have 95% analytical sensitivity in its detection of prions in vCJD brain and spleen spikes in plasma, and 99.5% diagnostic sensitivity in its detection of prions in normal human plasma samples. The Amorfix test was shown to meet the sensitivity requirement.

Dr. Bruce Evatt discussed the introduction of new blood screening tests. For regulatory agencies, key considerations include: pathogenicity, estimated prevalence among blood donors, the sensitivity and specificity of the proposed tests, the risks of not screening, and the costs of screening in terms of both dollars and impact on blood supply.

Chris James gave an overview of recent vCJD developments in the United Kingdom, the impact on patients, and the measures taken to try communicate timely, accurate information on vCJD transmissibility and risks.

Innovations and Updates

The final session presented some of the innovative research and programs for the development of new and better forms of treatment for people with inherited bleeding disorders. Dr. Dorthe Viuff discussed several projects ongoing with Novo Nordisk that aim to improve treatments for people with hemophilia who have developed inhibitors. These projects include development of a recombinant factor VIIa (rFVIIa) product; subcutaneously administered factor concentrate; long-acting rFVIIa derivative; fast-acting rFVIIa analogue; and research to develop recombinant factor VIII, IX, and XIII.

Dr. Glenn Pierce discussed the use of fusion protein technology using the neonatal Fc receptor (FcRn) to transport factor VIII and IX proteins. Preclinical pharmacokinetic studies of the recombinant factor IX Fc fusion in a variety of animal models demonstrated a three to fourfold increase in half-life compared to recombinant factor IX products.

Jeffrey Lawrence presented the advances in development of recombinant porcine factor VIII (OBI-1) by Ipsen. Ipsen is now planning two Phase III clinical trials to examine the safety, efficacy and pharmacokinetics of OBI-1 in the treatment of severe and life-threatening bleeds in patients with congenital hemophilia A with inhibitors, and the treatment of acute bleeding episodes in patients with acquired hemophilia A.

Dr. Clive Dash gave an overview of the steps and challenges involved in the development and licensing by Bio Products Laboratory (BPL) of a high-purity plasma-derived factor X concentrate for the treatment of factor X deficiency.

Dr. Lutz Bonacker described several factor products at different stages of research and development, and licensing and marketing by CSL Behring, including factor I/fibrinogen concentrate for the treatment of congenital fibrinogen deficiency and recombinant factor IX fusion proteins (rFIX-FP).

Key Points from the Sixth Global Forum

WFH president Mark Skinner recapped some of the key themes and discussions at this forum:

- It is essential to gather robust data and evidence support the ongoing work to advance hemophilia care and provide a foundation for confronting emerging challenges.
- More research is needed on the outcomes from different approaches to prophylaxis in order to determine optimal dose and regimen.
- HTA and CER serve as a warning for the global bleeding disorders community on possible threats to hemophilia care in the coming years.
- The creation of a streamlined pathway for regulatory approval of biologics holds both potential benefits and risks for the people with rare disorders.
- The WFH has a strong commitment to advance inhibitors research and facilitate international data harmonization.
- Transmission of vCJD infection through plasma-derived products is an ongoing concern that raises many implications in terms of testing and screening.
- Innovative programs and research initiatives on novel therapies are ongoing and show promising potential to improve treatment for hemophilia and other bleeding disorders.

Opening Remarks

Claudia Black, executive director and CEO of the World Federation of Hemophilia (WFH), welcomed participants from around the world to the Sixth WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders. “This meeting keeps growing and it clearly reflects the growing interest in global discussion and debate on issues related to treatment and care for people with hemophilia and other inherited bleeding disorders,” she said. She acknowledged vital financial support from the Global Forum’s key sponsors: the Public Health Agency of Canada, Canadian Blood Services, Héma-Québec, Ministère des Relations internationales (Québec Ministry of International Relations) and Ministère de la Santé et des Services sociaux, (Québec Ministry of Health and Social Services.)

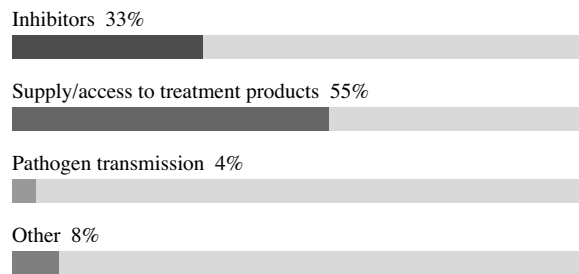
Global Forum 2009 marked the 10th anniversary of the biennial meeting and drew its highest attendance yet, 176 participants from more than 30 countries. “The participants at this meeting truly reflect the WFH’s winning coalition of patients, medical and healthcare professionals, government leaders, and corporate partners,” said WFH president Mark W. Skinner. He noted the attendance of more than 20 Ministry of Health representatives and regulatory officials, adding, “This number continues to grow as we all work together to achieve our vision of Treatment For All.”

Throughout the forum, participants were polled on a range of questions to assess the perceptions and concerns within the bleeding disorders community related to key issues. The results from the first poll showed that inhibitors are now perceived as the biggest safety threat to patients, surpassing pathogen transmission, and price is seen as the biggest threat to product supply.

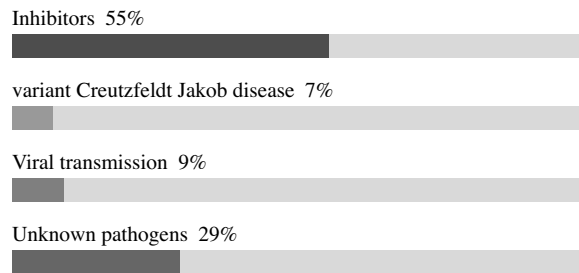
This is the 6th WFH Global Forum – including this forum, how many have you attended?

All six	9%
Four or five	6%
Two or three	28%
This is my first forum	57%

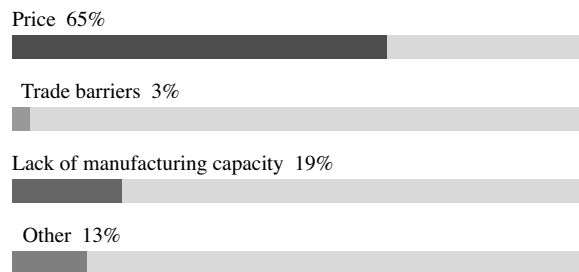
What do you think is the biggest threat to patients today?



What do you think is the biggest safety threat today?



What do you think is the biggest supply threat today?



Session 1: Global Factor Usage and Trends in Supply and Demand

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

Hemophilia care involves many key players—hemophilia treatment centre personnel, healthcare funders and policymakers, the clotting factor concentrate industry, regulatory agencies, and patient organizations—who work together to provide the best possible care for people with hemophilia given the healthcare system and resources available to them. Multidisciplinary care is extremely important in hemophilia care but clotting factor concentrates and the way they are used clearly play the most critical role in a patient's life, Dr. Alok Srivastava said. The treatment regimens currently used worldwide are on-demand therapy, given to treat serious and life-threatening bleeds, and a progressive range of prophylaxis regimens (short-term prophylaxis, late/delayed secondary prophylaxis, early secondary prophylaxis, primary prophylaxis), given to minimize joint damage, enable participation in the normal activities of daily life and physical exercise, and enable full community integration.

There are a number of critical questions regarding supply, availability and usage of treatment products for people with bleeding disorders: What is the current supply of factor? How is factor usage distributed throughout the world? How much supply should there ideally be now and in the future? How much supply is there likely to be in the near future? The opening session would provide an overall picture of the global market for factor concentrates, and forecasts related to possible changes in supply and availability on the horizon.

Factor Usage – Global Data

JEFFREY STONEBRAKER, DEPARTMENT OF MANAGEMENT, NORTH CAROLINA STATE UNIVERSITY, USA

Health, social, and economic indicators from the World Bank, World Health Organization and United Nations all strongly correlate with the standpoint that the critical measure of lifespan for people with hemophilia is factor concentrate use, stated Dr. Jeffrey Stonebraker. He presented findings from recent studies on worldwide factor use and hemophilia A prevalence.

The first study examined factor VIII use in 104 countries from 1996 to 2006 and variations in factor VIII use across national economies. The research results will be published in an upcoming article in *Haemophilia* titled, "A study of factor VIII use around the world." Factor use was examined from both the overall industry perspective of factor VIII use per capita and the patient perspective of factor VIII use per person with hemophilia, towards gaining insight on some of the supply and demand implications in terms of public policy, healthcare planning, and industry production planning. Data was obtained from The Marketing Research Bureau (MRB), an independent firm that specializes in market research related to blood and plasma products, and the World Federation of Hemophilia. MRB obtains data from industry, distributors, hospitals and governments; it does not collect data from countries every year. The WFH collects yearly data from national hemophilia organizations through the annual WFH Global Survey (supplemented with data from other sources); not all countries provide data every year.

The two sets of data were used to generate descriptive statistics including means, standard deviations and coefficients of variation. Regression analysis and analysis of variances in factor VIII by economic classification were also done, using the five economic classifications defined by the World Bank: high income OECD (Organisation for Economic Co-operation for Development), high income non-OECD, upper-middle income, lower-middle income, and low income. Although there was some variability between the two sets of data, the means (average annual per capita factor VIII use) were not very statistically different. The data also showed that in the majority of countries (67 of 104) factor VIII use is less than 1 International Unit (IU) per capita, which is considered the minimum amount of clotting factor needed to provide life-saving treatment. Furthermore, the study confirmed that per capita factor VIII use varies by national economies.

Regression analysis using a sample of five countries, one from each economic classification, was done to measure annual growth in factor VIII use over the 11-year period. The countries selected were: the United States (high income OECD), Singapore (high income non-OECD), Bulgaria (upper-middle income), Colombia (lower-middle income), and India (low income). Per capita factor VIII use in most of these countries increased steadily throughout this period; however, the high income countries consistently consumed greater amounts of factor VIII than the lower income countries and factor use by higher income countries also increased at faster rates than in the lower income countries.

Analysis of the global data on factor VIII use from 1996 to 2006 found that mean factor VIII use (IUs per capita) was significantly different for each economic classification. Furthermore, some countries – Iceland, Slovenia, Hungary, the Slovak Republic, and Iran – had unusually high per capita factor VIII use compared to the other countries within their economic classifications. The researchers hypothesize in their paper about possible reasons for these outliers; a few papers have been published on Iran’s experiences and the other countries were encouraged to share their perspectives.

Dr. Stonebraker also described the results from a prevalence study carried out in tandem with the study on per capita factor use, using the same data. The findings will be published in *Haemophilia* in an article titled, “A study of variations in the reported hemophilia A prevalence around the world.” This study found significant variability in the reported hemophilia A prevalence across the different economic classifications over the 1996 to 2006 time period, even in the high income economic classification. The majority of countries are consuming less than 1 IU per capita (estimated to be 20,000 IUs per person with hemophilia A). However, some countries have unusually high factor VIII use per person with hemophilia A compared to the other countries in their economic classifications. For example, the United States, Germany, Guatemala and Eritrea all have substantially higher factor VIII use per person with hemophilia A than the mean of their economic classifications. In some cases this may be because factor VIII is also used to treat von Willebrand disease.

Reported factor VIII use varies significantly different across national economies. The trends suggest that factor VIII use per person with hemophilia A is increasing with increasing economic capacities, and at faster rates in countries consuming more than 1 IU per capita (20,000 IUs per person with hemophilia A). “Higher factor VIII use per person with hemophilia A can be an indication of different things – better healthcare delivery, over treatment, or over-reporting of use due to under-reporting of the number of people with hemophilia A,” Dr. Stonebraker said. “Therefore, to understand the policymaking implications, we need to understand the treatment modalities used in each country for prophylaxis, on-demand therapy, orthopedic surgery, and inhibitors.”

Is it possible to estimate the target level of demand and factor VIII use for individual countries? What would be the healthcare policy implications and the implications related to industry? As a starting point, it must be recognized that demand is not the same as supply and that past sales and historical demand for supply do not equal demand, Dr. Stonebraker said. "Demand is what the patients need and what the doctors want to give them—it is what is therapeutic. And while there are dollar and cost constraints, it is important for the hemophilia community to define the therapeutic demand and push towards it. However, estimating demand is not easy because you're always anchored by the past demand or use, and there's no clear consensus on the different treatment approaches for prophylaxis, episodic therapy, and immune tolerance induction therapy."

There is also broad variability in the reported prevalence of hemophilia A and the treatment modalities used in both developed and developing countries. Having this data is very important from several perspectives. From the industry perspective, it allows manufacturers to better estimate factor VIII needs and plan production levels. From the medical perspective, it allows physicians to provide more effective treatment regimens to people with hemophilia without worrying about supply constraints. From the healthcare and public policy perspective, it allows for better planning and allocation of national healthcare resources to treat hemophilia. And from the patient perspective, it allows the key players involved in hemophilia care to understand and better respond to the needs of people with hemophilia, he concluded.

Projected Trends in Supply and Demand

PATRICK ROBERT, MARKETING RESEARCH BUREAU, INC.

Potential changes to the supply of coagulation factors could occur should there be approval of intravenous immune globulins (IVIG) for the treatment of Alzheimer's disease, said Patrick Robert. He described possible scenarios and forecasts for 2015. Two clinical trials are currently underway to determine whether IVIG could be an effective treatment of early-stage Alzheimer's disease. "If this product gets approval for Alzheimer's disease, one can expect the demand for IVIG to grow considerably and therefore more plasma would be processed, and more byproducts of IVIG such as clotting factor concentrates and albumin would be produced," he said. "At this time, it is expected that approval could occur by 2012, and the demand for IVIG for Alzheimer's disease would be in full speed by 2015."

With IVIG as the driving market force, an estimated 26 million litres of plasma will be fractionated worldwide in 2009. The current projection, factoring in some degree of stabilization of economies around the world, is that plasma fractionation will increase to about 33 million litres in 2015. But if IVIG is approved for the treatment of Alzheimer's disease, it is expected that 38 million litres of plasma would be fractionated in 2015. This additional 5 million litres translates into a large quantity of factor VIII products. "In my view, the supply of clotting factors by 2015 will be quite ample, and there will be logistical problems with distribution of these products to patients around the world," he said.

The worldwide market for factor VIII concentrates in 2007 was about 6.2 billion IUs, comprising about 2.4 billion IUs of plasma-derived factor and 3.7 billion IUs of recombinant factor. North America and Western Europe had significantly higher factor usage than other regions, as well as stronger increases in usage.

Overall, a growing number of governments are allocating funds for factor concentrates for the treatment of hemophilia. The gap in factor VIII usage between the industrialized countries and the emerging countries, while remaining significant, has narrowed

somewhat over the years. In 1984, the Middle East and Africa region represented 1.1 per cent of global factor VIII consumption. In 1990, the region represented 2.5 per cent of global factor consumption – this increased to 6.5 per cent in 2003. A similar trend can be seen in Central and South America, which represented 1.4 per cent of global factor consumption in 1984, 2.9 per cent in 1990, and 5.9 per cent in 2003. However, a review of per capita factor VIII use in a selection of 13 countries from 1995 to 2005 found that growth in factor VIII usage was faster in the industrialized countries (United States, U.K., Hungary, Italy, Japan) than in the emerging markets (Brazil, Venezuela, Turkey, Mexico, Peru, Egypt, China).

Based on recent trends and annual growth rates for factor VIII usage in different regions, and taking into account specific conditions in each region such as access to care, funding, and treatment modalities, MRB forecasts that the global market for plasma-derived and recombinant factor VIII products will increase from 6.2 billion IUs in 2007 to 7.7 billion IUs in 2015. Furthermore, Mr. Robert noted that two companies are currently developing new recombinant factor VIII products and others are developing new recombinant factor IX products, therefore it is likely that more recombinant products will also be on the market by 2015. This M.R.B. forecast is based on a very conservative manufacturing yield of 120 IUs per litre of plasma, due to the fact that some fractionation plants in the world do not produce factor VIII.

Recombinant factor products are currently used mainly in North America, Western Europe, Japan, and Australia. Recombinant products are starting to make inroads in emerging markets, with some degree of penetration in the Middle East, Central and South America, and Asia Pacific, but usage is not expected to grow as much as with plasma-derived products. “The price difference between the recombinant and plasma-derived products makes it difficult for quite a number of countries to afford recombinant factor.”

The forecast for factor VIII supply would change significantly if approval of IVIG for the treatment of Alzheimer’s disease were to occur in 2012, with the full impact manifesting in 2015. “Additional plasma would be processed, which in turn will mean more factor VIII produced. There would be an additional 90 metric tons of IVIG used for Alzheimer’s disease treatment, increasing from 80 metric tons in 2008 to 150 metric tons in 2015.” With this forecast, the global market for plasma-derived and recombinant factor VIII products would grow from 6.2 billion IU in 2007 to 9.3 billion IU in 2015.

However, the worldwide plasma fractionation throughput, regardless of whether or not IVIG is approved for Alzheimer’s treatment, would increase from 26 million litres to 33 million. “The plasma industry might not be able to process more than an additional 5 million litres for technical reasons, such as manufacturing capacity plant size, and economic reasons because the manufacturers will find themselves with enormous quantities of factor VIII, factor IX and albumin which they will probably have some difficulties in selling.”

Still, he predicted that there will be an ample supply of factor VIII in 2015 which will improve access to care for many patients with hemophilia and other bleeding disorders, particularly those in countries that so far had have limited access to factor products.

Discussion

Charles Waller of the Plasma Proteins Therapeutics Association (PPTA) noted that neither of the presentations touched on the potential impact of the global economic downturn and the constraints that governments will be under in the coming decade or longer. “The early signs in Europe are that the governments are sharpening their pencils on what can

they really afford, and whether to try get to the highest standard of prophylactic care or look at more affordable levels of care. It's implicit that the WFH can really compel governments to provide progressive levels of treatment, but it needs to be more explicit to all the stakeholders represented here that we really need be very vigilant in the coming years."

The products made through plasma processing are lifesavers and it is very hard for governments or healthcare providers to take away a life-saving product once it's been approved and prescribed—this is especially true for clotting factor concentrates, Mr. Robert said.

In some parts of the world, the generation of more plasma for IVIG will not necessarily lead to more supply of factor VIII as there is a tendency these days for nationally based fractionators to set limitations on provisional and surplus amounts of factor VIII, said Albert Farrugia of the PPTA. For example, Australia and Canada are both countries that supply plasma for fractionation and have highly developed hemophilia supply economies that are predominantly recombinant, and both currently discard a lot of factor VIII. With nationally based fractionation systems, particularly in Europe, there is a risk that a lot of factor VIII could be generated but will not actually be able to be utilized.

A key question is how is demand being created, Dr. Srivastava said. In 1996, at the World Hemophilia Congress in Dublin, 1 IU per capita was considered reasonable care and 3 IUs per capita considered good care. Over the past 12 years, standards have shifted such that 3 IUs is today deemed reasonable care and 5 or 6 IUs the ideal target.

For most countries, cost is the driving factor in terms of use of clotting factor concentrates, noted Bruce Evatt. Will the increasing availability of factor products due to the introduction of new therapies or IVIG approval for Alzheimer's treatment reduce the costs? If the costs remain the same, the supply growth rates may not meet the expectations in terms of the potential markets that would be accessed.

Mr. Robert replied that come 2015, IVIG will continue to carry the brunt of the cost because it would be the driving force, then it will be up to the manufacturers of plasma-derived proteins to allocate the costs to the other products, which will carry some of the cost but less than they do today.

Dr. Srivastava noted that the current concept of the cost of recombinant products could change in the near future given that there are many more manufacturers working to develop new recombinant products that would be more available at costs that more people can afford. This would change the dynamics of the entire distribution of recombinant products as well as the focus on plasma-derived therapy in many of the developing countries.

Participants were polled on a series of questions on the main determinant influencing choice of clotting factor concentrates in developed and developing countries. In comparing the results, Mr. Skinner noted that the majority of participants felt that evidence-based treatment protocols should be the main determinant. "To me the model of care in the developed countries really is much more of an individualized decision than what the literature says it should be—it involves tailoring the decision to what's right for each patient," he said. "The paradigm in most developed countries is that the patient and the physician work together to figure out what the treatment protocol should be and what the patient is willing to accept in terms of care, as well as its affordability. It will not always be about moving towards purely evidence-based decisions, because then you're not really treating the individual patient but just treating the disease as whole, moving people along."

What in your view is the main determinant of the choice of clotting factor concentrates (type-recombinant vs. plasma-derived and dose) in developed countries?

Opinion/practice of the treating physician	46%
Opinion of the person with hemophil	13%
Access and availability of clotting factor concentrates	23%
Evidence-based protocols for replacement therapy in hemophilia	14%
Attempt to match the highest reported doses	1%
None of the above	2%

What in your view is the main determinant of the choice of clotting factor concentrates (type-recombinant vs. plasma-derived and dose) in developing countries?

Opinion/practice of the treating physician	8%
Opinion of the person with hemophilia	0%
Access and availability of clotting factor concentrates	83%
Evidence-based protocols for replacement therapy in hemophilia	2%
Attempt to match the highest reported doses	2%
None of the above	5%

What in your view should be the main determinant of the choice of clotting factor concentrates (type - recombinant vs. plasma-derived and dose) in developed countries?

Opinion/practice of the treating physician	17%
Opinion of the person with hemophilia	16%
Access and availability of clotting factor concentrates	6%
Evidence-based protocols for replacement therapy in hemophilia	59%
Attempt to match the highest reported doses	0%
None of the above	2%

What in your view should be the main determinant of the choice of clotting factor concentrates (type-recombinant vs. plasma-derived and dose) in developing countries?

Opinion/practice of the treating physician	9%
Opinion of the person with hemophilia	2%
Access and availability of clotting factor concentrates	24%
Evidence-based protocols for replacement therapy in hemophilia	63%
Attempt to match the highest reported doses	2%
None of the above	0%

In your view today, which of these estimates of the total quantity of clotting factor concentrate per capita is likely to provide optimal care for people with hemophilia in any country?

1-2 IU per capita	4%
3-4 IU per capita	15%
5-6 IU per capita	31%
7-8 IU per capita	32%
9-10 IU per capita	12%
None	5%

Session 2: Prophylaxis Models

CHAIR: ALISON STREET, VICE-PRESIDENT MEDICAL, WORLD FEDERATION OF HEMOPHILIA

This session focused on the medical-scientific paradigm of prophylaxis, current evidence on the musculoskeletal and functional outcomes of different protocols, and ongoing studies and future research needs on key issues such as which regimen provides the best long-term outcomes, when is the best time to start and stop prophylaxis, how to assess and tailor patient-specific programs and a proposed framework for implementing and evaluating cost-effective and efficacious use of prophylaxis in developing countries.

Prophylaxis for Severe Hemophilia: the Dutch Experience

KATHELIJN FISCHER, HEMATOLOGIST, VAN CREVELDKLINIEK, UTRECHT, THE NETHERLANDS

Dr. Kathelijn Fischer gave an overview of the evolution of the prophylactic regimen developed at the Van Creveld hemophilia centre from establishment in 1969. In the initial years, the approach to treatment was prudent and sparing. Treatment was administered on the basis of bleeding patterns instead of target trough levels. Treatment was started after the first joint bleed, with dosage increased for bleeding episodes, and discontinued if the dose was low and bleeds were rare. Overall, treatment has intensified over the decades.

The current regimen sets out distinct parameters for assessing short- and long-term outcomes and treatment cost. Short-term outcomes are measured by annual number of joint bleeds, while longer-term outcomes are assessed using the Hemophilia Joint Health Score and the Pettersson radiological score. The Pettersson score tends to be more sensitive than the clinical score and detects earlier joint changes. Treatment cost is calculated from annual clotting factor use.

Treatment has intensified over the last 30 years. Prophylaxis is now started at a much earlier age, and the prophylactic dose has doubled from 16 IUs per kilogram per week to 33 IUs per kilogram per week. At the same time, the average number of joint bleeds per year for patients on prophylaxis decreased from 7.7 bleeds to 2.8 bleeds, and Pettersson scores have improved. These outcomes suggest that more intensive treatment yields better results.

While early prophylaxis is shown to be more effective, it is important to start treatment at the point in time that best optimizes outcomes, risks, and resource use. A review of the available data shows that the age of onset of joint bleeding varies widely (0.2 to 5.8 years) and suggests that the “golden window of opportunity” for starting prophylaxis is any time before the third bleed. Research also shows that after the first joint bleed, with each year of delay in introducing prophylaxis treatment, Pettersson scores progressively worsen by 8%, independent of age of bleeding onset, and dose.

The current Van Creveld protocol starts with a dosage of 500 IUs once per week once the first joint bleed or first severe bleed has occurred. After any subsequent severe bleed or joint bleed, the frequency of treatment is increased to 500 IUs twice weekly until bleeding is controlled and then lowered to 250 IUs three times a week. Treatment is individually tailored to deal with breakthrough bleeds.

Dr. Fischer presented data comparing outcomes of hemophilia patients in the Netherlands to outcomes in Sweden. The Dutch start prophylaxis after one or two bleeds with a weekly dose which is adjusted based on subsequent bleeding episodes. It is discontinued only in adults who have a mild bleeding phenotype. The Swedes on average start prophylaxis at an earlier age and use a higher dose. The clinical and Pettersson scores were not significantly different; however, once results were adjusted for age, it did appear that the Swedish cohort had a significantly larger proportion of patients who were bleed-free for more than three years.

Another critical question is whether or not prophylaxis should be administered lifelong. A joint Danish-Dutch study compared the results of patients with severe hemophilia without inhibitors who permanently stopped prophylaxis. These patients, born between 1970 and 1980, were followed for 3.6 years after discontinuing prophylaxis. While the Pettersson scores of the two cohorts were similar and comparable, on average the patients no longer on prophylaxis had slightly more joint bleeds per year than patients on continuous prophylaxis (3.2 and 1.8 bleeds per year, respectively). The Dutch patients who discontinued prophylaxis had a milder phenotype, started treatment slightly earlier, and were treated with higher doses. There were also statistically relevant differences in the clinical scores.

Dr. Fischer concluded by emphasizing the importance of continuing to assess and compare the outcomes from the different protocols and regimens in order to determine the most effective and efficacious use of prophylaxis. Short-term outcomes such as clotting factor consumption, treatment regimens, health-related quality of life, sports and social activities, and missed days of school or work should be assessed every year. Assessment using the Hemophilia Joint Health Score and the Pettersson score should be done every five years.

Prophylaxis: The Canadian Experience

VICTOR BLANCHETTE, HEMATOLOGIST, HOSPITAL FOR SICK CHILDREN, TORONTO, CANADA

Dr. Blanchette presented an overview of the Canadian Dose-Escalation Primary Prophylaxis Study and compared some of its findings with the U.S. Joint Outcome Study.

Both were started around the same time with harmonized entry criteria. The U.S. study, initiated in 1996, was a prospective randomized controlled trial that compared full-dose prophylaxis with enhanced episodic therapy, and has now ended. The Canadian study, initiated in 1997, is a prospective single-arm dose-escalation primary prophylaxis trial and is ongoing.

The Canadian study is following children with severe hemophilia A (defined as factor levels below 2 per cent) who were enrolled between 1 and 2.5 years of age with normal joints (based on a modified WFH orthopedic score) and normal radiographic scores (based on the WFH joint score). The study protocol involves three steps with dose escalation according to bleeding pattern and defined levels of unacceptable bleeding:

- Step 1 – Patients started on 50 IU/kg once weekly.
- Step 2 – Escalation to 30 IU/kg twice weekly.
- Step 3 – Escalation to 25 IU/kg every two days (minimum three times weekly).

The criteria for dose escalation are:

- Three or more bleeds into a single joint over a consecutive three-month period;
- Four or more significant soft tissue or joint bleeds (into any number of joints) over a consecutive three-month period;
- Five or more bleeds into any single joint while on the same dose of factor therapy.

Breakthrough joint bleeds are treated with additional factor therapy consisting of 40 IU/kg on the first day and 20 IU/kg on the second and fourth days, which is significantly more treatment than most regimens, Dr. Blanchette noted.

The initial cohort of 25 children has expanded over the years; there are currently 56 children from 11 hemophilia treatment centres across Canada enrolled in study. The median duration of follow-up thus far is 4.6 years; some patients have been followed for over 10 years. As the study has progressed, some of the children have moved from once weekly doses to twice-weekly doses (median age of 4.1 years) and some onto full doses (median age of 9.7 years). The expectation is that more children will move to full doses as they grow older and become more active. The most common reason for dose-escalation has been bleeds into the index joints (elbows, knees and ankles) and significant soft tissue bleeds in a consecutive three-month period. The most common types of bleeds early on are knee bleeds, which occur when babies start crawling around.

Magnetic resonance imaging (MRI) of patients with a history of joint bleeds, performed on average at 8 years of age, detected early osteochondral changes ranging from cartilage loss, subchondral cysts and bony abnormalities in 50 per cent of children. In comparison, osteochondral changes were detected by MRI in only 7 per cent of the patients enrolled in the U.S. Joint Outcome Study. MRI of patients with no history of bleeding showed no osteochondral changes but detected some soft tissue changes such as synovial hypertrophy and hemosiderin deposits.

The use of central venous access devices (Port-a-Catheters) was much higher in the U.S. study, over 80 per cent of patients, compared to 37 per cent of patients the Canadian study.

The significance of some of the differences between the U.S. and Canadian studies may not be apparent until the longer term, Dr. Blanchette said. For example, while early osteochondral changes were detected in many more Canadian children, the functional outcomes might not be as significantly different at 15 or 20 years of age. Continued follow-up of the Canadian cohort is warranted.

The effectiveness of primary prophylaxis regimens is influenced by many complex factors such as the individual patient's compliance, activity profile, and pharmacokinetics. Future studies to more clearly examine these variables on the outcome of primary prophylaxis regimens are needed.

Models for Prophylaxis: Can It Be Done in Developing Countries?

ALOK SRIVASTAVA, HEMATOLOGIST, CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

In developing countries, cost and limited availability of factor concentrates continue to be the most critical challenges in hemophilia care and patients have largely not had access to prophylaxis. However, a broader analysis of the available data suggests that there might be opportunities to make low-dose prophylaxis regimens possible in some developing countries with limited amounts of factor concentrates, said Alok Srivastava.

Numerous studies show the range of outcomes obtained from different treatment approaches and regimens developed over the last three decades. The most basic level of care is on-demand treatment for life-threatening bleeds. Short-term or secondary prophylaxis in adolescents or adults offers a notable reduction in arthropathy and disability. Late secondary prophylaxis also reduces arthropathy and enables participation in the normal physical activities of daily life. Finally, early secondary and primary prophylaxis allow people with hemophilia to live nearly normal lives.

Early prophylaxis regimens in the 1970s consisted of doses as low as 900 IU/kg annually, and according to studies did not have a major impact on number of bleeds or Pettersson scores. However, studies demonstrate that in the 1980s, the use of increased doses in prophylaxis resulted in significantly improved Pettersson scores over the longer term and fewer bleeds. A 2003 European study comparing outcomes from different dosage prophylaxis protocols (van den Berg et al.) demonstrated that patients in the Netherlands given intermediate-dose prophylaxis (around 1,828 IU/kg annually) had better Pettersson scores at age 20, in the range of 5 to 10, compared with patients in France given on-demand therapy (1,634 IU/kg), whose scores ranged from 15 to 20. Clinical and radiological outcomes improve with higher levels of factor and early introduction of prophylaxis which is superior to on-demand treatment.

Dr. Srivastava presented findings from the Musculoskeletal Function in Hemophilia in the Developing World Study (MUSFIH), which reported musculoskeletal outcomes (clinical, radiological and functional) in 234 children with severe hemophilia receiving varying levels of factor replacement therapy. Ten centres in nine developing countries participated in the study: Argentina, Brazil, Egypt, India, Iran, Singapore, South Africa, Thailand, and Venezuela. The study results indicate that while on-demand treatment successfully controls bleeds, reduces pain, and increases survival, it is not able to prevent the development of joint damage by 20 years of age. This raises the question whether on-demand therapy is truly the best possible course of treatment for patients in developing countries, even those with low factor usage in the range of 1–2 IU per capita, and suggests that there could be a better alternative.

Analysis of cumulative retrospective data on factor usage and bleeding profiles did not show consistency between the amount of factor used for on-demand treatment and number of bleeds, nor between factor use and clinical joint scores and in the long-term, on-demand treatment does not yield positive musculoskeletal outcomes. Until a threshold level of factor availability to implement prophylaxis is achieved or the available supply is used in a different way musculoskeletal outcomes are unlikely to improve.

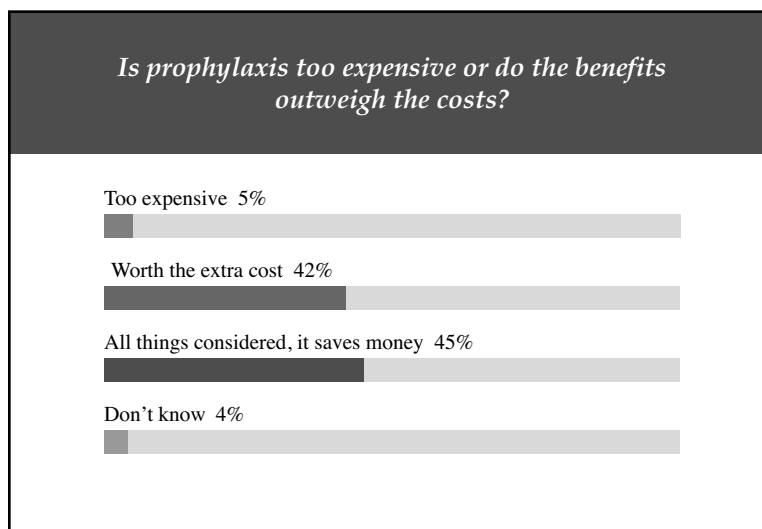
By extrapolation from population data from developing countries, it is estimated that it would be possible for countries with as little as 1 IU per capita available to provide low-dose prophylaxis to children with severe hemophilia A introducing a regimen of 10 IU/kg weekly. In countries with 2 IU per capita of factor available, this dose could be doubled.

With a low-dose prophylaxis approach, there would ultimately be a greater amount of factor concentrate available for treating severe hemophilia because of the reduction in bleeds and need for on-demand factor treatment, and exclusion of patients with mild phenotypes and inhibitors from prophylaxis.

There is good evidence that significant reductions in hemarthroses can be achieved with low doses of prophylactic factor therapy. Thus countries that already use 1 to 2 IU per capita could consider shifting from on-demand therapy to early low-dose prophylaxis. The primary and most significant challenge however remains to convince healthcare authorities, physicians and patients that this novel low-dose approach to prophylaxis is worth attempting. It is critical to continue to assess the outcomes of different treatment approaches and regimens to determine which ones provide maximum effectiveness in countries where factor supply is limited.

Discussion

The audience was polled on the following question:



Dr. Street commented that most participants felt that on-demand treatment is not successful from the perspective of long-term musculoskeletal function and outcomes. There remains, however, a lack of data on prophylaxis use and outcomes in adults and much more research is needed to obtain a clearer understanding of the outcomes.

WFH president Mark Skinner asked panelists to imagine, from the perspective of a health minister in a developing country, having a choice between introducing recombinant products or introducing prophylaxis and taking in to account the costs— which choice would have a greater impact on long-term outcomes? Dr. Fischer replied that prophylaxis would clearly provide better long-term outcomes.

Dr. Srivastava noted that there are different cohorts within every country that receive different levels of care for various reasons. For example in India, some patients who have government-supported care can now receive recombinant products. If changing to recombinant products means that less factor would be available, it makes sense to stick to the safest lower cost products, but if supplemental funding is available, then no harm is done by introducing more expensive recombinant products.

Dr. Blanchette stressed the importance of starting prophylaxis with an available safe concentrate. However, he said, it won't be possible to judge effectiveness unless tested on large patient populations. There is a whole range of critically important information that can only be gathered through international cooperation and collaboration.

Dr. Farrugia asked Dr. Blanchette whether the different results between the U.S. and Canadian studies were due to specific product differences. Dr. Blanchette said the differences were more likely related to the sensitivity of the endpoints used; for example, when the definition of failure is based on early MRI changes. Further study design and more data may be necessary.

Dr. Makris asked panelists to reflect on their experiences with children growing up on prophylaxis. In his experience, arthropathy is still a problem in children today, which may be due to the fact that they are more active and engage in more sports and physical activities than children in the past. Dr. Blanchette said there are two important issues: compliance and patients' pharmacokinetics. There is evidence that when clotting factor levels are below 1%, the bleeding risk is higher. However, data suggests that there are also other factors that affect bleeding risk. For example, some of the regimens for prophylaxis were devised for administration in the medical setting during clinic hours, rather than being intended for home use, and as a result, there were three-day gaps in treatment over weekends, which may not be the most therapeutically beneficial schedule.

Dr. Evatt asked how panelists would advise ministries of health in assessing product safety for prophylaxis. Dr. Srivastava said he would advise them to purchase the largest possible quantity of a safe factor product – the treatment decisions then rest with the individual physicians on how to make the best use of the amount of factor available for their patients. Even when only 1 to 2 U per capita are available, it might make sense to use it to provide lower-dose prophylaxis for children. It's important, however, to ensure that the product is reliably available.

Chair Alison Street concluded the session by stressing the importance of comprehensive care programs, particularly in countries where prophylaxis programs are just starting. Those teams must include social workers, physiotherapists, nurses, laboratory scientists and clinicians noting that it doesn't matter how much product is available if it is not used properly.

Session 3: Economics and Outcome Assessments Threats to Care in a Tightening Economy?

CHAIR: BRIAN O'MAHONY, CEO, IRISH HAEMOPHILIA SOCIETY

Many countries with well-resourced healthcare systems currently provide an “open-ended” supply of factor concentrates for hemophilia treatment, with prophylaxis available for children and many adults, and no restrictions on clinicians or clinical freedom, said Brian O'Mahony. Though the annual cost of care per patient can be quite high, outcome assessments of hemophilia care have largely not been done. However, with the current global economic recession, the environment is changing. “Healthcare budgets are under threat in many countries, and hemophilia as a high-cost condition is going to be increasingly examined by governments and their health economists,” he cautioned.

Mr. O'Mahony presented data showing the great disparities in access to factor VIII concentrates among the European Union's 27 member states. Sweden's per capita factor VIII usage is 23 times that of Romania. Per capita factor usage by Gross Domestic Product (GDP) also varies considerably. In November 2009, Sweden will be the first country to initiate a full health technology assessment on hemophilia, which will focus on prophylaxis. It will be important for the global inherited bleeding disorders community to keep watch of how the process unfolds, he said.

Economics and Comparative Effectiveness: Threats to Care?

MICHAEL LAUER, DIRECTOR OF CARDIOVASCULAR SCIENCES, NATIONAL HEART, BLOOD AND LUNG INSTITUTE, USA

Comparative effectiveness research (CER), rather than a threat to health care, should be viewed as an important component of evidence-based medicine, said Dr. Michael Lauer. “We have seen many instances in the history of medicine and in modern medicine where medical therapies were widely promoted and used, but then found upon further investigation to be inappropriate or harmful.”

For example, thalidomide was promoted as a “wonder drug” for the treatment of morning sickness during pregnancy but was later found to cause birth defects. Anti-arrhythmic drugs were widely used to prevent sudden cardiac death for patients with heart disease, but in fact anti-arrhythmics increased mortality rates. Hormone replacement therapy was thought to be a powerful way to prevent cardiovascular disease in post-menopausal women but turned out to increase the risk of cancer and stroke.

Many different factors can lead to the wide use and acceptance of medical therapies that later turn out to be inappropriate, Dr. Lauer said. These include scientific belief, overreliance on logic rather than experience, strong personalities who support certain approaches, the hopes of desperately ill patients, hype, and financial gain. “Practical comparative effectiveness study by our own profession could potentially have saved many lives,” he suggested. Of course, many medical therapies have proven successful. The common feature among successful medical therapies is that clinical trials were performed, Dr. Lauer said.

Comparative effectiveness research and health economics have become predominant issues in the United States, as signaled by President Barack Obama when he declared in his inaugural address that U.S. health care is too costly. This was soon followed by the U.S. stimulus bill introduced in February 2009, which dedicates \$1.1 billion for comparative effectiveness research. The current climate emphasizes three core concepts in economics, Dr. Lauer said. Resources are scarce and finite in supply, choices and comparisons are critical, and decisions come at a cost to other opportunities. “The goal of comparative effectiveness in health care is not to minimize expenditures but to maximize effectiveness,” he said.

The United States currently spends over \$7,000 on health care per capita, on the whole about 17 per cent of its total GDP, and the costs are rapidly rising, Dr. Lauer noted. Healthcare inputs are much greater than in other countries. For example, the United States performs the most CT scans per capita globally, and furthermore pays tenfold more (\$616) than Japan (\$62) per CT scan. A similar phenomenon is seen within the United States, with enormous differences in per capita Medicare spending (government-funded health insurance coverage to people who are age 65 or older or who meet other special criteria) in different regions. “From both national and global perspectives, health care is excessively costly, inputs are excessive and pricey, costs are highly variable, and variations in healthcare spending do not appear to correlate with outcomes,” he said.

Comparative effectiveness research can help address these problems by making valid comparisons of different treatment options or strategies, Dr. Lauer said. This involves studying data from actual patients to measure treatment outcomes such as length of life, quality of life, and costs. There is currently intense debate in the United States as to whether cost-effective analysis should be part of this research, and whether it should be a national priority, Dr. Lauer said. Some of the arguments in favour of cost-effective analysis are based on the belief that healthcare inflation is unsustainable. Arguments against integrating cost-effective analysis are that it is complex, and that industry-funded analyses would be biased.

In his view, the disparities in costs and clinical practices in different regions point to a need for comparative effectiveness research that includes cost-effective analysis. Moreover, while cost-effective analysis is often synonymous with rationing of health care services, he asserted, “This rationing already exists—40 million people in the United States do not have health insurance and health insurance companies can deny treatments for patients for a variety of reasons.”

Comparative effectiveness research may be a way to address major gaps in evidence, and provide research that is directly informative as it is based on practice and policy. Cost-effective analysis as a subset of this type of research would address the issue of value and getting the maximum “bang for the buck,” he concluded.

Funding for Hemophilia Care in Europe: A Taste of Things to Come?

ADAM HUTCHINGS, HEALTH ECONOMIST, GLOBAL MARKET ACCESS SOLUTIONS

Hemophilia care in Western Europe has been very well funded by national healthcare systems in recent decades, with consistent improvements in treatment and levels of factor usage, noted Adam Hutchings. Routine prophylaxis for children is now the standard of care and people with hemophilia receive an excellent level of care at hemophilia treatment centres. There also continues to be a lot of hemophilia research. “The picture until now has

been a good one – payers have not looked towards hemophilia as an area to make cuts in funding,” he said. However, he noted that across European healthcare systems, every other disease area has been subject to cost-constraint mechanisms in recent years. Some of these mechanisms have resulted in very contentious decisions by European payers that sometimes mean patients may have a shorter life expectancy and reduced quality of life, he said.

Hemophilia has not been subject to such constraint mechanisms for many reasons including the fact that it is a rare, congenital bleeding disorder, and that it can be a very severe condition. There is also some sympathy among payers towards the hemophilia community because of the HIV and hepatitis C (HCV) infections that occurred in the mid-1980s and early 1990s due to contaminated blood products. Almost all new products that have been launched in Europe in the last 10 years are available to prescribers, including expensive new treatments where other treatments already exist, and almost all patients who require orthopedic surgery, including patients with inhibitors, have access to surgery, he noted.

However, there are many reasons why the hemophilia community should have cause for concern, he said. European public finances are deteriorating as countries struggle with the economic recession, the burden of bailing out their financial institutions, and rising social security payments. Many face fiscal deficits in the realm of 7 to 8 per cent of their GDP; most economists predict big cuts in European public expenditures in the near future. “Health care will have to bear its share of the brunt – we can expect to see healthcare budgets cut by 10 to 20 per cent over the next few years, and it’s unreasonable to expect hemophilia to be immune from the impact,” he said.

Another concern is that the special status of factor concentrates for hemophilia treatment may diminish, he said. Hemophilia used to be one of a very small number of orphan diseases, which together represented a relatively small amount of the total healthcare budget. New treatments for rare diseases are coming to market as a result of orphan drug legislation introduced earlier this decade, and the aggregate cost of treating orphan diseases is rising. Hemophilia is not likely to be exempt from payer mechanisms to constrain pharmaceutical expenditures, especially given that factor concentrates are among the most expensive treatment products in many European countries and the annual cost of care per hemophilia patient can be quite high, he said.

The cost-effectiveness of prophylaxis compared to on-demand therapy could also come under payer scrutiny. Mr. Hutchings noted that the estimates of the cost per quality-adjusted life year with prophylaxis are very different and wide ranging, from \$50,000 to \$2.7 million per quality-adjusted life year. “Some of the treatment practices that we consider as the absolute gold standard of care could be questioned by payers and may not necessarily be endorsed,” he said.

Currently, the biggest single concern and possible threat to hemophilia care in Europe is health technology assessment (HTA), which involves evaluating the benefits and costs of particular treatments as a way to make difficult funding decisions. The National Institute for Health and Clinical Excellence in the U.K. has been engaged in HTA for some years and similar assessments are underway in Scandinavia and Germany. Furthermore, Sweden’s Dental and Pharmaceutical Benefits Agency is about to initiate the first HTA of hemophilia.

Mr. Hutchings described a range of possible outcomes from health technology assessment of hemophilia treatment. In Sweden’s case, given the country’s excellent hemophilia care standards, the best possible outcome would be maintenance of the status quo. But if,

instead, a certain factor concentrate, group of factor concentrates, or treatment protocol gets deemed not cost-effective and no longer eligible for reimbursement, it would effectively mean that patients would have to switch to cheaper therapies, he noted.

Another possible threat is that payers could decide that hemophilia care has been sufficiently funded, and cap hemophilia budgets. “This throws the responsibility of making difficult treatment decisions to physicians, such as whether to reduce factor usage, use cheaper products, or restrict patients from having surgical interventions in certain situations,” he noted.

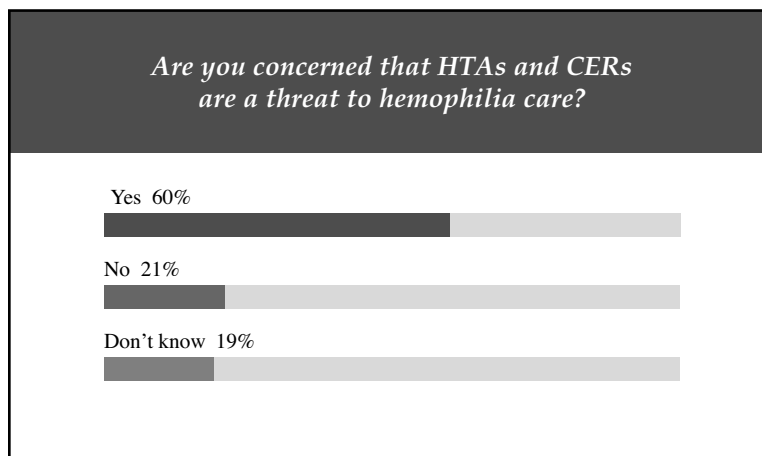
Finally, national tenders for the purchase of factor concentrates could be either a possible threat or potential benefit. A national tender can be a very good process to bring together hemophilia patients, physicians, and payers to make informed decisions about product selection, availability, and supply. However, a tender that is done poorly, simply to reduce healthcare costs and without any concern for product quality or the security of the supply, can endanger quality of care in the country.

The hemophilia community needs to be vigilant and defend hemophilia funding from potential threats from payers, he said. “Get a good understanding of local funding systems, find out who the decision-makers are, and be prepared. A good way to anticipate threats to hemophilia care is to watch trends in other disease areas as well as in neighbouring countries.”

Patient organizations and clinicians will also need to educate healthcare decision-makers and payers about hemophilia and the important benefits that patients currently receive from the investments in hemophilia care. Having good data on patient benefits is crucial. Payers conducting health technology assessments generally look at evidence from randomized controlled trials, clinical and long-term data on impacts (for example, bleed frequency, joint damage, disability or mortality), and costs of care. However, they are also interested in data regarding quality of life. “Communicate to your members the importance of collaborating to collect good data through quality of life questionnaires and surveys. It can involve a lot of effort but it is so important towards maintaining the quality and levels of hemophilia care, particularly in the face of HTAs,” he said.

Discussion

Participants were polled on the following questions:



Is it appropriate to have a separate review process or panel for rare diseases so that their unique needs can be taken into consideration?

Yes	84%
No	10%
Don't know	7%

Who needs to gather data to make the case for hemophilia when dealing with HTAs or CERs?

Clinicians	11%
Industry	2%
Patient organizations	4%
All of the above	83%

Chair Brian O'Mahony noted that it is vitally important that industry, clinicians and patient organizations separately gather evidence-based data as well as observational and experiential data on the benefits of prophylaxis, in order to be prepared for health technology assessment or comparative effectiveness research related to hemophilia.

There is a great need for more data on outcomes for patients who receive on-demand therapy, said Kathelijn Fischer. Outcome assessment of patients on prophylaxis should be performed alongside a cohort of patients who receive on-demand treatment, in order to be able to compare outcomes such as quality of life, days lost from work, and orthopedic procedures, she added.

Paula Bolton-Maggs emphasized the importance of being prepared. "We need to have a well-planned evidence base and identify the clinical experts who are going to represent the hemophilia community, and make sure they are ready for the process," she said.

WFH president Mark Skinner noted that health technology assessments and comparative effectiveness research require evidence that meets certain scientific and ethical standards and a burden of proof, which can be difficult to obtain with rare diseases which have a very low prevalence and affect a very small number of people. It is often not possible to conduct a clinical trial regionally or in one country alone—clinical trials may need to be on a global basis. What can be done in the absence of evidence and in the absence of the ability to produce the evidence in a scientifically ethical way?

Even when there are such constraints, it is reasonable to insist on getting the highest quality evidence possible, Dr. Lauer said. "Some disease communities have been very successful at this. For example, although childhood cancers are relatively rare, the pediatric oncology community has done a much better job than the adult oncology community has in creating a research culture whereby the vast majority of children with cancer are enrolled in clinical research protocols. The result is that every patient becomes a real learning experience and contributes to high-quality science. It's very difficult to do, but it shows how tight collaborations can potentially result in the best quality of care for patients."

Bruce Evatt challenged the idea the health technology assessments and comparative effectiveness research could have positive outcomes for public health. “It is a useful tool for economists and healthcare planners but it’s too subjective and it’s also a young science – and whether or not it’s good science is certainly debatable at this point.”

Dr. Srivastava suggested that rather than comparing on-demand therapy with prophylaxis, comparative effectiveness research should compare different prophylaxis doses and regimens. He also cautioned that quality of life alone should not be the measurement used for assessing outcomes, particularly in this disease area. “It’s possible to have people with bad joints who report a very good quality of life, and people with good joints who report a bad quality of life, so quality of life should not be assessed in isolation. It must be combined with assessment of musculoskeletal status.”

Do you expect to see a decrease in the standard of hemophilia care in the next five years due to payer actions?

Yes	18%
No	70%
Don't Know	12%

Session 4: A Streamlined Regulatory Pathway for Biologics

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

This session presented different perspectives on the development of biosimilars (also referred to as generic or follow-on biologics, subsequent entry biologics, follow-on protein products, multisource products, therapeutically equivalent products, and interchangeable, substitutable or comparable products) and the concept of a streamlined regulatory pathway for biosimilars.

The development of a streamlined regulatory pathway for biosimilars involves potential risks, opportunities and benefits for the bleeding disorders community, Mark Skinner said. There are a number of complex issues and challenges that need to be addressed:

- Scientific data needed for evidence-based decisions.
- Clinical safety and efficacy requirements.
- Regulatory and legal issues surrounding orphan drug laws and patent protections.
- Economic impacts on industry, healthcare costs and consumer access.
- Market implications on supply, innovation, and price.

In the United States, the debate surrounding the development of biosimilars has become more prominent in recent years. In March 2003, the National Organization for Rare Disorders (NORD) Conference on Exploring the Pathway to Generic Biologics examined whether these medicines would be safe, appropriate and feasible alternatives to biologics that are currently in use. Regulation of generic biologics was a key topic of debate at the Plasma Forum held in June 2004 by Plasma Protein Therapeutics Association (PPTA), and in September 2004 the U.S. Food and Drug Administration held the first FDA Workshop on follow-on biologics.

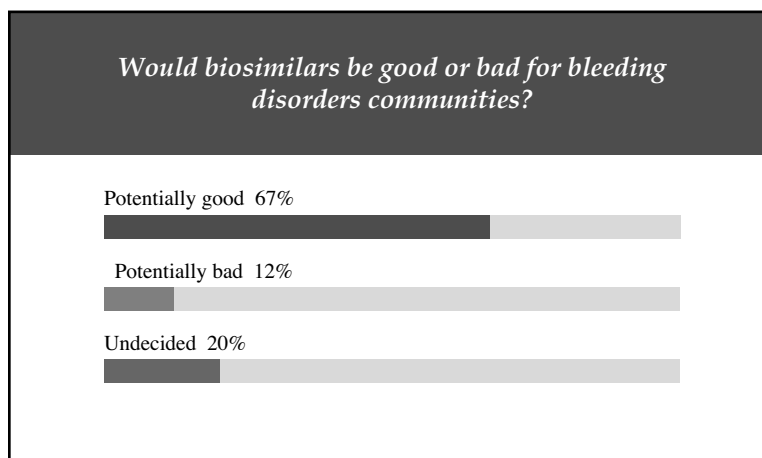
Discussion around the topic intensified over the past year as the issue of healthcare reform in the U.S. came to the forefront. Correspondence between NORD and the Office of the President indicated that there was support for the creation of a regulatory pathway for biosimilars and agreement that these products could potentially lower drug costs for patients and healthcare providers, improve access to treatments, and stimulate innovation of new and improved therapies. When U.S. President Barack Obama released his fiscal budget and healthcare reform bill, they contained provisions on the licensure pathway for biosimilars aimed at streamlining the approval process for biosimilars to facilitate the timely introduction of safe and affordable biosimilars to the market.

The PPTA subsequently released its position on the proposed biosimilars legislation, in the white paper, "Patients Who Depend on Plasma Protein Therapies Need Legislative Protection from Unpredictable Risks to which an Abbreviated Product Approval Pathway Could Expose Them." However, not all manufacturers were united in their opposition to biosimilars. At the time of announcing the acquisition of Wyeth, the CEO of Pfizer endorsed the development of generic biologics, and a July 2009 newspaper advertisement from the Pharmaceutical Care Management Association called for access to safe and affordable biogenerics and featured a child with hemophilia to illustrate the need for

life-saving biogeneric drugs. In August 2009, the National Hemophilia Foundation (NHF) issued a policy statement supporting streamlined regulatory approval pathway for biosimilars, provided that there be protections for the end users of the products.

In summary, Mr. Skinner explained that the U.S. experience has particular importance because drug approval by the FDA, as well as by the European Medicines Agency (EMA), usually results in rapid approval by regulatory agencies in many other countries.

The audience was polled on the following question:



To Be or Not to Be: Follow-on Biologics

DIANE EDQUIST DORMAN, VP PUBLIC POLICY, NATIONAL ORGANIZATION FOR RARE DISORDERS, U.S.A.

The National Organization for Rare Disorders (NORD) was formed by parents and support groups who advocated for research and funding for orphan drugs, which are pharmaceuticals for treating rare diseases and diseases that have a small market. It was founded in 1983 with the passage of the Orphan Drugs Act. Diane Edquist Dorman gave an overview of the organization and its efforts in lobbying for access to orphan drugs and advocating the creation of a streamlined regulatory pathway for follow-on biologics (i.e., biosimilars, generic biologics).

NORD is dedicated to the identification, treatment, and cure of rare disorders. The organization has a range of objectives:

- Serve the general public, voluntary organizations, healthcare professionals, industry, and policymakers.
- Promote education, advocacy, research, and service.
- Act as liaison to federal agencies and the biopharmaceutical and medical device industries.
- Formulate positions on relevant public policy issues.
- Participate or take leadership roles in coalitions.

Ms. Dorman provided some basic facts on rare diseases and drug costs in the U.S. There are over 7,000 known rare diseases, which affect about 30 million people in the U.S. About 50 per cent of these rare diseases cause motor, sensory, or intellectual deficiencies, while 20 per cent cause chronic pain and many result in death. About 75 per cent of the people who have rare diseases are children, with disease usually appearing before two years of age, and about one-third of the children die before five years of age.

Traditional drugs on average cost about US\$1,200 per year. Biologics are more complex drugs and on average cost about US\$71,600 per year. About 21 per cent of orphan drugs are biologics. There are 343 orphan drugs being used in the U.S. to treat 12 million people, but many millions of others with medical conditions remain untreated as there are no therapies available, she said.

Some orphan drugs cost US\$200,000 or more per year, and costs are expected to double in the near future. The high cost of orphan drug products are adversely affecting patients with rare diseases including hemophilia, as insurers are increasingly targeting orphan drugs and increasing the costs of co-payments or refusing to cover treatments, she said.

The National Organization for Rare Disorders has identified the following key goals and outcomes for the development and regulation of generic biologics:

- Safety and therapeutic outcomes that do not differ from innovator biologics.
- Fair and balanced approach to exclusivity.
- Transparent regulatory pathway.
- FDA authority and flexibility to determine scientific data and requirements for particular types of drugs.
- Decoupling of the litigation and review process.

There are many competing interests surrounding orphan drugs. Patients need products and doctors want the best possible care, while consumers worry about high costs and regulators and industry continue to grapple with patent and exclusivity issues. It's important to find a balance between access to innovative new therapies and access to lower cost therapies, she said. Industry must have incentives to develop new products but at the same time, lower orphan drug costs are needed so that patients and doctors actually have access to new innovations and treatments for the many rare and orphan diseases that are as yet untreatable, she concluded.

Biosimilars in the United States: Unique Challenges for Plasma Protein Therapies

JAY GREISSING, DIRECTOR, FEDERAL AFFAIRS, PLASMA PROTEIN THERAPEUTICS ASSOCIATION (PPTA)

The Plasma Protein Therapeutics Association (PPTA) is a global organization that represents companies that produce plasma-derived and recombinant therapies, referred to as plasma protein therapeutics. Jay Greissing outlined some of the issues and challenges related to an abbreviated pathway for the approval of biosimilars, from the perspective of manufacturers of biologics.

Biosimilars are not generic drugs, he emphasized. Conventional generic drugs are pharmaceuticals that are chemically identical to the original branded products, whereas biosimilars are similar to—but not the same as—the “innovator” biologics, he said.

Biologics are much more complex because they are derived or manufactured from human or animal proteins and must meet additional regulatory requirements towards ensuring safety and purity.

The proposed legislation to create an abbreviated approval pathway for biologics requires manufacturers to demonstrate that their biosimilar product has no clinically meaningful differences from the licensed biologic in terms of safety, purity, and potency. The objective of creating an abbreviated pathway for biologics is to provide incentives to companies to pursue development of new therapies, which in turn is expected to increase competition and innovation and thereby result in lower drug costs for patients.

However, Mr. Greissing reiterated that biologics are much more complex medicines than conventional pharmaceuticals – and therefore an abbreviated pathway such as the mechanism established 25 years ago for approval of generic pharmaceuticals (generally small molecule drugs) should not be expected for biosimilars. While savings in drug costs would undoubtedly be welcomed by the U.S. public, particularly the many patients who risk hitting their lifetime insurance cap for drug expenses, a critical question is whether the potential risks associated with an abbreviated process for biologics will be worth it in the long term, he said.

The manufacturing process for plasma-derived therapies is much more complex than that of conventional pharmaceuticals. There are both direct and indirect costs, including high production costs, due to strict standards and additional manufacturing steps, which are not required for non-biologic medicines – these factors affect which products are created from plasma in the protein fractionation process, Mr. Greissing noted. The process begins with collection of plasma, which is frozen and kept on a 60-day inventory hold, after which a number of very complex proteins are extracted from the plasma by fractionation. The factor VIII molecule is a very large polypeptide chain, and there are many steps in the manufacturing process including purification and viral reduction or inactivation. Every manufacturing step is critical and none of the products are interchangeable, as a patient may react differently to each product. The manufacturing process for recombinant products is equally complex, involving stabilization, purification, chromatography, and viral inactivation and reduction.

Mr. Greissing said that the European Medicines Agency (EMA) has stated that since biologics are highly complex proteins with complex manufacturing technologies, its position is that an abbreviated approval process for these types of drugs is not acceptable and biosimilars will be subjected to the same rigorous approval process as new biological products.

This issue has specific, critical implications for people with hemophilia, Mr. Greissing explained. One of the major adverse reactions in patients with hemophilia is the development of inhibitors to plasma protein therapies. There are both genetic risk factors (e.g., hemophilia severity, type of mutation, genotype) and treatment-related risk factors (e.g., previously untreated/first exposure, infusion regimen, product and manufacturing characteristics, product switching) associated with inhibitor development. Overall, inhibitors are an unpredictable risk. With biosimilar products, there are great uncertainties and unknowns about their risk of adverse events including inhibitor development. Given that treatment of inhibitors is very expensive, the risks and unknowns of biosimilars could offset the potential cost savings hoped for from biosimilars, he said.

There continue to be a number of points of contention surrounding biosimilars. These include how the non-patent market exclusivity period will affect biosimilars and whether it should include data exclusivity. The degree of potential cost savings is also not established. In addition, the bill only addresses immunogenicity in the context of interchangeability; there is no express provision on biosimilar immunogenicity risk.

At the present time, it is very difficult to weigh the benefits against the risks of an abbreviated regulatory pathway for biosimilars. The PPTA will continue to work to ensure that any biosimilars legislation makes patient safety the first priority, he concluded.

National Hemophilia Foundation's Principles for the Approval of Biosimilars

JOHANNA GRAY, NHF WASHINGTON REPRESENTATIVE, NATIONAL HEMOPHILIA FOUNDATION, U.S.

Johanna Gray presented an overview of the key principles identified by the U.S. National Hemophilia Foundation (NHF) regarding the creation of a regulatory pathway for the approval of biosimilars at the Food and Drug Administration (FDA). The concept of a regulatory approval process for biosimilars has been discussed for several years, but gained momentum this year as part of the political debate and public discourse on U.S. healthcare reform legislation. Two proposed legislative bills put forward to the U.S. Congress both contain a provision on creating a regulatory pathway for biosimilars, aiming to balance the need to provide incentives for industry to innovate and improve products with the capacity to provide patients with lower drug costs.

The NHF convened a panel of experts to review the implications of a regulatory pathway for biosimilars for the bleeding disorders community. Without taking an official position on either of the healthcare reform bills, the NHF supports the creation of a regulatory pathway for biosimilars while also identifying the following principles as crucial to any biosimilars legislation:

- Safety and efficacy – Given the history and challenges faced by the bleeding disorders community in the 1980s as a result of contaminated blood products, safety and efficacy must be the primary concern.
- Clinical trials – The regulatory approval process for biosimilars must require clinical trial data including assessment of immunogenicity in order to ensure the safety and efficacy of biosimilar products.
- Interchangeability – Substitution should not be permitted except with the consent of the patient and treating hematologist.
- Resources for FDA –The FDA must be given appropriate resources and authority to implement this new regulatory responsibility.
- Exclusivity period – U.S. regulations on exclusivity should be harmonized with standards in Europe.

There are a number of challenges being debated. There is disagreement on whether full clinical trials should be necessary for biosimilars and whether assessment of immunogenicity data should also be required; some argue that biosimilar manufacturers should be allowed to access and use the innovator data but this is a contentious issue. From the NHF's standpoint, clinical trials must be required in order to ensure that biosimilars are safe and effective, Ms. Gray said.

Interchangeability, whether insurance companies can switch a patient from one therapy to another at its discretion, is another critical issue for the U.S. bleeding disorders community. Typically, generic pharmaceuticals are thought to be substitutable. At this time, there is little consensus within the scientific community as to the resulting immunogenicity risk when randomly switching patients between products or product classes. However, people with bleeding disorders respond differently to innovator products, therefore the NHF feels that it is crucial that this treatment decision be left to a physician and patient.

Another contentious issue is length of the exclusivity for innovator products. The NHF recommends harmonization with the 10-year exclusivity period set out in EMEA regulations; however, consideration should be given to granting an additional two years of exclusivity for products that treat rare diseases, to give manufacturers incentive to pursue research and development of treatments for small populations.

Moving forward with the creation of a regulatory pathway for biosimilars, appropriate resources and increased funding must be provided to the FDA so that it can ensure the safety and efficacy of biosimilars under the new mandate, she concluded.

Discussion

The audience was polled on the following questions:

What would you need to see or know to take, prescribe, or purchase a biosimilar clotting factor concentrate? (Industry representatives were excluded from the vote.)

Immunogenicity studies	55%
Price comparison to innovator drug	2%
Wait to see clinical experiences of others	35%
Not sure	8%

Should human clinical trials be mandatory for all biosimilar clotting factor concentrates or should the regulatory authorities be given discretion to determine the extent to which such trials are needed?

Mandatory for all	55%
Allow regulatory discretion on case-by-case basis	42%
Not sure	2%

The biggest benefit of biosimilar clotting factor concentrates would be:

They will increase the available supply	18%
They will reduce price and make clotting factors more affordable	45%
They will foster competition and product innovation	24%
None of the above	13%

The biggest risk of biosimilar clotting factor concentrates would be:

They will destroy competition and product innovation	14%
They will put patients' health at risk	30%
They will reduce clinical freedom to prescribe brand-name clotting factors	21%
None of the above	35%

Industry concerns about biosimilars are driven by (all participants):

Fear of price and market competition	49%
Concerns about product safety	8%
Both a and b	39%
Neither a nor b	4%

Industry concerns about biosimilars are driven by (no industry participants voting):

Fear of price and market competition	70%
Concerns about product safety	0%
Both a and b	29%
Neither a nor b	2%

Albert Farrugia said there is inadequate information and understanding on this issue because the crucial term, “abbreviated regulatory pathway,” has not been well-defined. Clinical trials are at the crux of the debate. Abbreviation is not being proposed for any of the other complex safety and efficacy elements required for the regulatory approval process; the point of contention is whether or not biosimilar manufacturers need to carry out new clinical trials, which are the most expensive part of product development. The production of clotting factor concentrates involves many quality assurance measures and to ensure product safety – if the proposal is to somehow abbreviate that process, then this should be clearly spelled out, he said.

Ms. Dorman said that while the precise definition of the abbreviated regulatory pathway has yet to be determined by the FDA, the assumption at NORD is that clinical trials would be required. Moving forward, it is important for the FDA and other regulatory agencies to determine the precise definition and scientific requirements of the abbreviated regulatory pathway in conjunction with industry and patient groups.

Victor Blanchette stressed that robust clinical trials are expensive. Currently, the cost of clinical trials is being borne almost exclusively by industry. The per case reimbursement to clinicians covers only a small portion of the costs spent gathering information for trials. Other agencies who are partners in these issues should assist with the funding of clinical trials, he said. The U.S. National Institutes of Health is undertaking basic and translational research on new and rare diseases to examine how to help move products forward into later-stage clinical trials.

Dennis Jackman of CSL Behring stressed the importance of establishing an appropriate data exclusivity period, otherwise innovation and competition will be dampened.

Participants were polled again on whether biosimilars will be good or bad for bleeding disorders communities, to gauge whether opinions had changed following the presentations.

Would biosimilars be good or bad for bleeding disorders communities?

Potentially good	72%	(up 5%)
Potentially bad	14%	(up 2%)
Undecided	14%	(down 6%)

Session 5: Inhibitors Studies

Opportunities for Harmonization

CHAIR: MIKE SOUCIE, U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

The development of inhibitors to clotting factor is a serious complication and among the biggest challenges in hemophilia treatment today, said Mike Soucie. Inhibitor development has life-changing impacts for patients. Inhibitors reduce treatment efficacy and greatly increase the cost of patient care; consequently, risk of inhibitor development is a concern that can affect decisions about treatment such as when to start care. Inhibitors also present challenges for the development of new treatment products for hemophilia because it is very difficult to assess inhibitor risk during clinical trials, given the very small population of patients involved. Overall, there are still critical gaps in knowledge about the risk factors associated with inhibitor development.

In recent years, there have been efforts and progress made internationally to address the issues through the harmonization of protocols and data requirements for clinical studies. In 2003, a U.S. Food and Drug Administration (FDA) workshop on factor VIII inhibitors defined a number of key elements for standardization of clinical study design:

- Testing/measurement of inhibitor titers at a central lab.
- Tracking of number of exposure days.
- Genomic screening of inhibitor patients.
- Recording of product switching.
- Recording of any lack of effect (defined as increase in dose or frequency of dosing).
- International collaboration on inhibitor research and studies.

In 2006, an expert panel of the European Medicines Agency (EMA) identified similar guidelines and criteria for inhibitor studies:

- Detailed information on product exposure.
- Inhibitor testing with the Nijmegen method.
- Testing on regular basis (including prior to product switch and in response to a clinical indication of inhibitor).
- Analysis of hemophilia gene defect.
- International harmonization of datasets.

The International Society for Thrombosis and Hemostasis (ISTH) has also focused efforts on harmonization of data collection. In 2006, the ISTH FVIII and FIX Subcommittee Meeting looked at a comparison of U.S. and U.K. data elements and suggestions for harmonization and sharing of data instruments; and at the 2007 meeting, the U.K. and Germany presented a plan for harmonized data collection on inhibitors.

There are several challenges in inhibitor research and studies. Characterization and risk assessment of rare adverse events is methodologically difficult. Evaluation of treatment product risks using a probabilistic model is not always reliable. Clinical trial methodology can also be problematic because sample sizes are too small to adequately assess risk; assessment of risk factors tends to be incomplete. Moreover, randomization to the larger population is problematic.

There are also significant epidemiological challenges. Estimates of risk are based on probability, so absolute certainty is only possible by testing the entire population. The practical approach is to take a sample; however, this means that confidence about the study results is directly related to the sample size. The larger the sample, the more confidence and certainty there is in the study's findings and representative outcomes. Since hemophilia is a rare disorder, study populations are relatively small and widely distributed. Inhibitor cases are even more rare; they tend to occur in about 25 per cent of previously untreated patients and rarely develop in previously treated patients. Therefore, a major challenge of conducting inhibitors research is the need to study a large number of patients to obtain an adequate number of inhibitor cases. Furthermore, there are also a number of genetic factors linked to inhibitor risk such as gene mutation, immune modifiers, family history, and race, and environmental risk factors such as factor product, infusion circumstances, bleed severity, and age.

Several studies are underway around the world to examine various aspects of inhibitors. The objectives of this session were to provide information on the efforts made towards harmonization of inhibitor studies and identify opportunities and strategies for collaboration moving forward.

The audience was polled on the following questions:

Are you involved in a national or international study of inhibitors?

Yes	42%
No	58%

Which products are associated with a higher incidence of inhibitors?

Recombinant	42%
Plasma-derived	6%
Both equal	22%
Don't know	29%

In your opinion, how much data harmonization exists among national and international studies of inhibitors?

Very little	27%
Some	38%
A lot	6%
Don't know	28%

Adverse Event Monitoring: The UKHCDO and EUHASS systems

MIKE MAKRIS, HEMOPHILIA DIRECTOR, SHEFFIELD HEMOPHILIA AND THROMBOSIS CENTRE, ROYAL HALLAMSHIRE HOSPITAL, SHEFFIELD, U.K.

Mike Makris gave an overview of the adverse event monitoring system of the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) and the European Hemophilia Safety Surveillance (EUHASS) project.

The UKHCDO was established in 1968 and shortly after initiated the U.K. hemophilia registry. There are currently 26 comprehensive hemophilia care centres in the U.K. and 61 hemophilia treatment centres. Virtually all patients with bleeding disorders and their treatments are registered and followed from birth to death. In total, there are 23,637 registered patients with bleeding disorders. Of those, 6,303 have hemophilia A and 1,304 have hemophilia B.

The UKHCDO adverse event monitoring system was introduced more than 20 years ago. The following adverse events are tracked: HIV transmission; non-A, non-B or hepatitis C transmission; hepatitis B transmission; new inhibitor; thrombotic event/disseminated intravascular coagulation (DIC); transfusion reaction; other adverse event. The system currently involves three-month reporting and relies on the postal system but is in the process of being upgraded to an internet-based system with monthly reporting.

In 2007, there were 17 new inhibitors reported in the U.K. The overall cumulative data on incidence of inhibitors in the U.K. show the correlation between inhibitor development and disease severity. With both hemophilia A and B, inhibitors occurred far more often in patients with severe hemophilia than in patients with mild or moderate hemophilia; therefore, patients with severe hemophilia have an increased risk of inhibitor development.

Whenever a new inhibitor in a patient is reported, the UKHCDO requests the following additional information:

- Demographic information.
- Coagulation disorder, severity, and genotype if known.
- Any relatives with inhibitors.
- First inhibitor detection date and the reason for the test.
- Inhibitor value at first detection and maximum value.
- Any change in the baseline of factor VIII- or factor IX-coagulant (FVIII:C or FIX:C).
- Any change in bleeding pattern.
- Treatment protocol before inhibitor development.
- Time in chronological and exposure days from first dose to inhibitor development.

Event reporting is being harmonized with the European Hemophilia Safety Surveillance (EUHASS) project; however, UKHCDO will also be collecting additional data on inhibitors.

The European Hemophilia Safety Surveillance system is a multinational, prospective surveillance project, launched in 2008 as part of a three-year study that aims to establish a pharmacovigilance program to monitor treatment products for bleeding disorders. The study has enrolled 56 large hemophilia centres in 27 countries so far, and expects to have 70 sentinel centres by the end of 2009.

The EUHASS scheme monitors patients with the following bleeding disorders:

- All severities of hemophilia A and B.
- All types of VWD.
- Other rare disorders: fibrinogen defects; factor II, V, VII, X, XI, XIII deficiencies; combined factor deficiency factor V and VIII and combined factor II, VII, IX and X deficiency; alpha 2 anti-plasmin deficiency.
- Female carriers with low factor VIII and IX levels.

The EUHASS system is monitoring and collecting information on the following adverse events:

- Inhibitors.
- Allergic reactions.
- Transfusion transmitted infections.
- Thromboses (deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke), both related and unrelated to factor concentrate.
- Malignancies.
- Deaths.

Adverse events and data are reported live (as soon as they occur) or via quarterly reports produced within four weeks of each observation period, and cumulative data is reported annually by diagnosis and by clotting factor concentrate.

Event-specific data is submitted anonymously but soundex codes (unique anonymized identifiers) are used to avoid double reporting. The specific data collected includes:

- Patient's age, sex, diagnosis and disease severity.
- Name of treatment product(s) used.
- Single product or multiple product use.
- Total exposure days.
- First and second inhibitor levels.
- Assay used and cut-off.

The annual cumulative reports provide data on how many patients are registered; how many have severe disease, and of these, how many have had more than 50 treatment exposures and how many previously-treated patients have switched products in the last year; and adverse events related to specific coagulation treatment products.

Dr. Makris noted that participation is voluntary – hemophilia centres do not receive any funding to participate in the UKHCDO surveillance system and nor, for the most part, do centres taking part in the EUHASS study. This willingness to participate without funding and compensation underscores the commitment to collaborate on inhibitors studies in order to address the gaps in knowledge about inhibitor development, he said.

The PedNet Hemophilia Registry, RODIN Study and SIPPET Study

ELENA SANTAGOSTINO, HEMATOLOGIST, ANGELO BIANCHI BONOMI HAEMOPHILIA CENTRE, MILAN, ITALY

Elena Santagostino presented an overview of three ongoing initiatives to study inhibitor development in previously untreated patients (PUPs), since these patients have a higher risk of developing antibodies to factor concentrate

The European Paediatric Network for Hemophilia Management (PedNet) is an infrastructure for ongoing clinical research on children with hemophilia. Its aims are to share experiences of pediatric hemophilia care and facilitate basic and clinical research related to hemophilia treatment and outcomes. The network is made up of 21 hemophilia treatment centres in 14 European countries, whose patients are followed through the PedNet Hemophilia Registry.

The RODIN study is a satellite study of PedNet that is focused on research of determinants of inhibitor development among previously untreated patients with severe hemophilia A in Europe. The study design is similar to the PedNet registry but its objective focuses specifically on examining the associations of possible risk factors with the risk of inhibitor development among previously untreated patients with severe hemophilia A. The RODIN study also differs from PedNet in that it includes non-European centres and its enrolment is limited to previously untreated patients with severe hemophilia A; whereas all children with mild, moderate or severe hemophilia A or B are eligible to enroll in the PedNet registry.

The PedNet registry and RODIN study have a number of common elements:

- A specific assessment form is used at every outpatient clinic visit.
- Clinical data is collected during the first 75 exposure days.
- The treatment-related data reported include clotting factor infusions, medications, vaccinations, and infections.
- The patient data reported include factor VIII genotype, inhibitor tests, and factor VIII recovery rates.
- The primary aim is to identify clinically relevant inhibitor development, which is defined as at least 2 positive titers combined with a decreased in vivo factor VIII recovery (less than 66 percent of the expected value).
- A secondary aim is to identify high-titer inhibitor development, defined as the occurrence of a clinically relevant inhibitor with a peak titer >5 BU/mL.

PedNet has enrolled 662 patients including 398 patients with severe hemophilia. The RODIN study has registered 79 patients, all of whom have severe hemophilia A. The principal investigators and clinical epidemiologists of both these studies are collaborating very closely. Information from the studies is available online at www.pednet.nl and www.rodinstudy.eu.

In contrast to these adverse events monitoring systems, the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) study, on the other hand, is a randomized, open label clinical trial. The study's aim is to assess immunogenicity of factor VIII products by determining the incidence of inhibitor development in previously untreated and minimally blood-component-treated patients in the first 50 exposure days or first three years of enrollment (whichever comes first) to plasma-derived VWF/FVIII concentrates and recombinant factor VIII concentrates.

The study's secondary objectives are to evaluate a range of clinical and laboratory factors associated with inhibitor development. The clinical factors include:

- Age at first exposure.
- Treatment dose and regimen.
- Vaccinations, infections.
- Complications related to central venous catheters.
- Mode of childbirth delivery.
- Breast-feeding.

The laboratory factors include:

- Factor VIII gene defect.
- Factor VIII antigen (FVIII:Ag).
- VWF antigen (VWF:Ag) and VWF ristocetin cofactor activity (RcoF).
- Interleukin-10 gene (IL-10G), TNF-alpha and CTLA4 polymorphisms.
- HLA genotype.

The SIPPET enrolment criteria limit participation to patients with severe hemophilia A who were previously untreated or minimally exposed to clotting factor concentrates (fewer than five exposure days), under age 6, and without inhibitors at the time of enrolment. Patients will be randomized by country and treatment centre and randomly assigned to one of two arms:

- Recombinant arm: Products belonging to the class of recombinant FVIII concentrates not containing VWF; namely Recombinate® and Advate® by Baxter, Kogenate® by Bayer, and Refacto AF® by Wyeth.
- Plasma-derived FVIII/VWF arm: Products belonging to the class of plasma-derived FVIII concentrates containing VWF; namely Alphanate® and Fanhdi® by Grifols, Emoclot® by Kedrion, and Factane® by LFB.

The treatment regimens (prophylaxis or on-demand therapy) will be chosen by the local clinicians, and factor therapy for surgery is permitted. There are 80 centres from 26 countries involved in the study and a total of 300 patients will be enrolled.

The SIPPET study uses the following inhibitor definitions:

- Positive titer inhibitor: >0.4 BU/ml.
- High-responding inhibitor: peak >5BU/ml.
- Transient inhibitor: spontaneous disappearance within 6 months maintaining the same treatment regimen.

Inhibitors will be monitored locally and confirmed at the central laboratory in Milan, Italy. Patients receiving on-demand therapy will be tested every three to four exposure days or every three months (whichever comes first) until 20 exposure days. Patients on prophylaxis will be tested every 10 exposure days or every three months (whichever comes first) after 20 exposure days. After the appearance of an inhibitor, inhibitor titers will be monitored monthly for six months. Factor VIII epitope analysis will also be conducted at the central laboratory.

Overview of Hemophilia Inhibitor Genetics Study, Hemophilia Inhibitor PUP Study

DEBORAH BROWN, HEMATOLOGIST, UNIVERSITY OF TEXAS, HOUSTON, U.S.A.

Deborah Brown described two laboratory studies that have been designed with the capacity to be harmonized with clinical and epidemiological studies.

The Hemophilia Inhibitor Genetics Study (HIGS) is an investigator-driven study with three objectives:

- Determine the genetic factors associated with the development of inhibitors and response to antigenic challenge by factor VIII.
- Identify environmental factors that might increase the risk of inhibitor development.
- Explore genetic/environmental interactions that might increase the risk of inhibitor development.

The study is designed in three phases. Phase I is a linkage study between genetic markers and phenotype, for which investigators are currently seeking to enroll brother pairs, at least one of whom has an inhibitor, and their parents. Phase II will enroll a patient with an inhibitor, and his parents. Phase III will enroll unrelated hemophilia patients with and without inhibitors.

More than 26 countries are represented in the HIGS study. The clinical data will be collected retrospectively and will include:

- Date of birth and age at onset of treatment.
- Race/ethnicity.
- Presence of an infection or other illness at time first dose of factor was given.
- Current type of treatment (prophylaxis or on-demand).
- History of HIV or hepatitis C.
- History of hospitalization (for surgical procedure, injury, or infection).

Specific inhibitor-related data will also be collected:

- Number of exposure days prior to inhibitor development.
- Type(s) of clotting factor used prior to inhibitor development.
- Date and method of inhibitor detection.
- Inhibitor titer at detection, peak and current titer.
- Initiation of immune tolerance (type of regimen, successful or not).

The genotype testing will examine 14,626 single nucleotide polymorphisms from 1,081 genes. The family studies will allow researchers to examine the DNA variations and link them to phenotype, thus this a potentially powerful study, Dr. Brown said. The study is underway and has enrolled nearly 1,000 patients and family members.

The Hemophilia Inhibitors PUP Study (HIPS), which Dr. Brown is leading with co-principal investigator Elena Santagostino, will examine immune system response in previously untreated patients with hemophilia who have severe A. The aims include:

- Analyze and functionally characterize factor VIII-specific T cells during the first 50 exposure days to a single factor VIII product.
- Monitor regulatory T cells (Treg) during the first 50 exposure days.
- Analyze antibody subclasses of anti-factor VIII antibodies.

Inhibitors can occur when a patient is exposed to factor VIII for the first time; the factor VIII may be identified as a foreign protein. The immune system processes the peptide or protein as an antigen, resulting in the activation of both B and T cells. The B cells go on to activate plasma cells, creating antibodies, which then identify and neutralize the factor VIII. The activated T cells upon first exposure are either suppressor or regulatory cells.

The study's hypotheses are that:

- The type of factor VIII-specific T cell that is activated during early exposure determines the immune system's "decision" to develop inhibitors or not.
- Patients who do not develop inhibitors have a high proportion of regulatory T cells (Treg) during early exposure, compared to those who develop inhibitors.
- Infections and immunizations at the time of factor VIII treatment reduce the proportion of Treg cells and encourage the induction of factor VIII-specific T cells that drive antibody responses.
- The type of factor VIII mutation is related to the type of T cell that is activated during early exposure.
- The sub-class of anti-factor VIII antibodies that develop is associated with the type of factor VIII-specific T cell that is activated during early exposure.

Treg cells are very hard to isolate, and there have not been many studies in this area. The HIPS study is a multi-centre, international, prospective, natural history study. A single recombinant factor VIII product will be used and the type of treatment will be selected by the investigator. Participants will be followed for 50 exposure days or three years, whichever comes first. Study participants will be previously untreated babies with hemophilia, whose factor levels are below one per cent.

The clinical data collected will include ethnicity/race, family history, medication, infusion dates, bleeding episodes, and adverse events. Since this is a prospective study, it will be possible to examine the immune system even before the first exposure, as well as at key points during exposure, Dr. Brown said. Inhibitor testing will be done through a central laboratory and will include a Bethesda titer assay and an ELISA assay for anti-factor VIII antibodies.

The study's steering committee includes researchers involved in many other major studies, which should make it easier to harmonize the data, she concluded.

Pilot Study of Surveillance for Inhibitors in the U.S.

MIKE SOUCIE, U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

Mike Soucie presented an overview of a Pilot Study of Surveillance for Inhibitors in the U.S. This study provides increased support for data collectors to collect more detailed information about inhibitors. It will explore methodologies for collecting required treatment and bleeding information. Centralized inhibitor testing and hemophilia gene sequencing will take place at the U.S. Centers for Disease Control. Twelve hemophilia treatment centres have been selected to participate in the study and each will enroll 50 patients.

The U.S. Pilot Study is a prospective cohort study that will enroll patients of all ages with hemophilia A or B. There will be ongoing data collection about exposure to treatment and complete gene sequencing. Inhibitor testing will take place annually, prior to an anticipated product switch, or at any time there are clinical indications.

Since 2006, 850 people have been enrolled in the study. The mean age of participants in the study is 22 years, with a range from 6 months to 87 years. Most of the patients, 81 per cent, have factor VIII deficiency, while 18 per cent have factor IX deficiencies. About 13 per cent of the patients enrolled have a history of an inhibitor.

To date, the study has identified 241 unique factor VIII mutations. Nearly half of the mutations (117) are not reported in HAMSTeRS (the Hemophilia A Mutations Database) or other publications. In addition, 48 unique factor IX mutations have been found, 8 of which are not reported in the hemophilia B mutation database.

Discussion

The audience was polled on the following questions:

What is the most significant barrier to successful data harmonization?

Lack of data sources	11%
Variable treatment and testing practices	49%
Lack of international collaboration	26%
Lack of scientific consensus	15%

In your opinion, what measure would be most effective to improve data harmonization?

Enhanced investigator communication	14%
An international consensus statement	27%
An international steering committee	21%
Standardization of treatment and testing	38%

A high level of harmonization is already taking place in inhibitors studies, from surveillance projects to very detailed clinical and research studies, Dr. Soucie said. The studies vary widely in size and design, with data collected both prospectively and retrospectively. All collect detailed information about particular factor products and exposure levels. Some but not all of the studies specify frequency of inhibitor testing, and not all used centralized laboratories. In addition, the patient background information collected varies from study to study. He invited participants to share their views on the potential for further harmonization and ways in which inconsistencies could be overcome.

Kathelijjn Fischer said the key issue, that was not addressed in the presentations, is the definition of an inhibitor. An important priority is to establish consensus on the definition of “clinically relevant inhibitor.” She recommended including less than two-thirds of anticipated recovery as part of the criteria.

Dr. Santagostino said it is important for clinicians to have clear information on the definition of clinically relevant inhibitors. At the same time, to clarify the data, it is also necessary to include low-titer and transient inhibitors. Even though transient inhibitors may be less clinically relevant, it is important to know their prevalence, effects, and exposure.

Albert Farrugia expressed concern that there are many inhibitor trials taking place, which might be depleting the number of previously untreated patients available for other important studies and clinical trials. Dr. Brown agreed that there may be some “clinical trial fatigue,” particularly for patients, but said there is not much overlap among the different studies presented during this session. Dr. Santagostino added that the same study groups can also be used to gather other critical information and that the trials involving previously untreated patients should each be used to its maximum potential.

Alok Srivastava said the ISTH FVIII and FIX Subcommittee is aware of the lack of consensus on definitions and has proposed the formation of working groups to arrive at common definitions, to provide good starting points for moving forward on harmonization.

Alison Street, WFH VP medical, noted that the WFH Medical Advisory Board has established a research subcommittee and the WFH is very committed to helping facilitate and achieve harmonization of inhibitor studies.

Session 6: variant Creutzfeldt Jakob Disease - Transmission, Testing and Risk Assessments

CHAIR: DAVID PAGE, EXECUTIVE DIRECTOR, CANADIAN HEMOPHILIA SOCIETY

Over the past two decades there has been continuing concern about the possible risk of transmission of variant Creutzfeldt Jakob disease (vCJD) through blood products, especially in the United Kingdom, the epicenter of the outbreak, said David Page. While there have been three cases of apparent vCJD transmission via fresh blood transfusion, until very recently there has been no known case of transmission via plasma-derived products. Then in December 2008, U.K. health authorities reported that a person with hemophilia, who had never shown symptoms of vCJD infection, had been found post-mortem to have vCJD-related prions in his spleen; following further investigation, it has been announced that there was 99 per cent probability that the infection was transmitted by clotting factor concentrates.

It is anticipated that a vCJD screening test able to detect prions in blood donations may become available in the near future. However, the prospect of vCJD testing has many implications for both blood donors and recipients of plasma products. This session would focus on current understanding of the risks of vCJD transmission from plasma-derived products, especially for people with hemophilia; development of a vCJD screening test; lessons learned from the introduction of HIV testing in the mid-1980s; and planning and design of screening programs.

General Features of Risk Assessments for vCJD in Hemophilia Products

ALBERT FARRUGIA, SENIOR DIRECTOR, GLOBAL ACCESS, PLASMA PROTEIN THERAPEUTICS ASSOCIATION

Risk assessments on vCJD transmission through plasma derivatives generate varying outputs depending on factors such as the mathematical model and input parameters used and the local natural environment, said Albert Farrugia. He described some vCJD risk assessments conducted to date and their outcomes, and current gaps in the science.

A number of key input parameters affect outputs on vCJD risk. These include number of blood/plasma donations pooled in the production process; volume of blood/plasma donation; number of units of product from the production process (yield), and estimated amount of product to which the patient is exposed. Some inputs are still very uncertain, such as the amount of transmissible spongiform encephalopathy (TSE) infectivity in a population and in blood, and the extent of TSE clearance that is achieved during the production process.

A key uncertainty is the prevalence of vCJD in a population, including within the U.K. Currently, the main assumption is that anyone who lived in U.K. during the period that bovine spongiform encephalopathy (BSE) penetrated the food supply is infected. This resonates with biopsy studies that have been done in the U.K. on appendectomy and tonsillectomy specimens. Other important issues are subclinical infection, which has been measured in people who were infected and died from vCJD; and supplemental infection,

given that the biopsy studies suggest that there are likely people who have vCJD but are not aware that they are infected. Furthermore, TSE infectivity in plasma is not well understood.

A number of countries have performed vCJD risk assessments in the past decade based on different mathematical models, input parameters, and assumptions. In brief:

- The Australian risk assessment in 2002 by the Therapeutic Goods Administration included subclinical infection and yielded outputs that suggested “somewhat alarming” potential risk of vCJD infection from factor VIII concentrates that led to policy decisions regarding product access through non-plasma means.
- The French risk assessment in 2000 was based on the assumption that there is no endogenous infectivity in France (so any infectivity was attributed to contaminated beef or bone meal produced in the U.K. during the period of the BSE epidemic) and found that factor VIII products are of the highest risk but the absolute risk is extremely small.
- The risk assessment by the Canadian Public Health Agency in 2005 looked at prevalence in terms of number of actual clinical cases and did not include subclinical infection; it also showed that the relative risk is highest with factor VIII but actual risk is very small.
- The risk assessment model by the U.S. FDA in 2006 examined the impact of different factors on vCJD risk using data on factor VIII utilization from the Centers for Disease Control (CDC). The most significant factors increasing risk were the amount of factor VIII product used by a patient, route of exposure, and infectivity in blood. The log reduction of vCJD agent during the production process was critical to reducing risk.

The risk assessments have produced varying estimates but regardless of the parameters used, they all agree on two important points—that plasma-derived factor VIII products has the highest possible relative risk and clearance during the production process is most critical to actually minimizing risk as much as possible. However, the amount of clearance varies enormously between production processes and between products and the clearance itself is largely “fortuitous” rather than the result of specific elimination steps introduced for vCJD.

There are still large gaps in the science. In the case of the U.K. patient with hemophilia found in post-mortem autopsy to have signs of vCJD infection, prionic infection was detected in only 1 of 20 histology samples taken from the spleen. On the other hand, another post-mortem investigation of a patient who had been treated with IVIG manufactured with implicated batches of plasma found no vCJD transmission, likely because the Cohn fractionation process for IVIG clears out enormous amounts of infectivity, he said. Such uncertainties are the reason why manufacturers and health authorities take precautionary measures to try do all they can to reduce the risks of transmission and infectivity.

Screening tests for vCJD tests are very important for blood transfusion recipients and the hemophilia community but even with vCJD screening, TSE infectivity will still be a very critical issue for all biologics, Dr. Farrugia emphasized. Recombinant products are not zero risk either; a 2004 study demonstrated that the common laboratory cell lines used to

generate other pharmaceuticals are also susceptible to prionic infection. “There can be no compromise on the issue of clearance—let nobody one think that the introduction of a vCJD test means we can relax any of the measures that are now place in the manufacture of factor VIII nor the research for a way to make sure that prions are cleared,” he concluded.

Blood Screening Assay for the Detection of Prions Based on Epitope Protection Technology

GEORGE ADAMS, PRESIDENT & CEO, AMORFIX LIFE SCIENCES LTD., TORONTO, CANADA

Over the last five years, Amorfix Life Sciences has been working to develop a routine blood screening test for vCJD prions using epitope protection technology. Dr. George Adams gave an overview of the EP-vCJD™ Blood Screening Assay, the promising results to date from large-scale studies done in the United Kingdom and France, and further studies that will soon be underway.

A vCJD prion is an aggregated misfolded protein. The misfold occurs when a vCJD prion infects a normal protein; over time, more and more misfolded prions develop and accumulate in the body. A key challenge to developing a screening test for vCJD is that only a very small amount of prions is found in blood—one prion per one million normal proteins. “It’s like trying to see a star on a sunny day,” he said. However, a much higher amount of prions has been found in brain tissue; in one patient who died from vCJD, about 15 to 20 per cent of the brain proteins were found to be prionic.

Amorfix’s proprietary epitope protection technology uses peroxydinitrite to chemically mask normal proteins in a blood sample; the misfolded prion proteins are unaffected and can then be detected using a conventional sensitive and rapid immunoassay. The EP-vCJD blood screening assay is an ELISA test with five possible points of identification for prion proteins and is effective because it is actually two and a half tests in one. It is a high-throughput blood screening test with ISO certification, an 18-month shelf life, and processing time of 3.5 hours.

The European Commission’s draft Common Technical Specifications and guidance document on CE marking for vCJD specify that an assay must have 95% analytical sensitivity in its detection of prions in vCJD brain and spleen spikes in plasma, and 99.5% diagnostic sensitivity in its detection of prions in normal human plasma samples. (By comparison, the criteria for the HIV test introduced in 1984 were 95% specificity and 95% sensitivity.) In 2006, the U.K. government provided a panel of negative and positive spike samples to all the manufacturers working to develop a vCJD test. The Amorfix test was shown to meet the sensitivity requirement.

Over 2008 and 2009, Amorfix conducted a series of studies using the EP-vCJD blood screening test at blood centres in the U.K. (1,540 samples tested in Edinburgh) and large-scale studies in France (20,265 in Alsace, 13,251 in Montpellier). The studies demonstrated 100% sensitivity and 99.9% to 100% specificity, with no false positives, he reported. Testing with protein misfolding cyclic amplification (PCMA) blood samples demonstrated that the EP-vCJD test was able to accurately detect infectious prions. Testing on scrapie-positive sheep that had been either naturally infected or inoculated at birth was able to detect both subclinical and preclinical forms of prion disease. Amorfix is now working on a confirmatory test for large-scale testing on samples of 10% vCJD brain homogenate spiked in 10 mL of normal human plasma.

Amorfix is also moving towards expanding the studies to a third blood centre in France and initiating a large-scale study to test 10,000 samples in the U.K to confirm the French results, to be followed by a U.K. prevalence study on 50,000 samples. Future goals include large-scale testing of high-risk groups such as people with hemophilia and recipients of multiple blood transfusions.

Screening Tests for New Agents

DR. BRUCE EVATT, HEMATOLOGIST, ATLANTA, GEORGIA

The introduction of new blood screening tests generally raises a number of issues and implications for regulatory agencies, physicians and patients that must be carefully considered in the planning of programs, said Dr. Bruce Evatt. Any new screening test for pathogenic agents has three basic applications—screening, diagnosis, and scientific research. For regulatory agencies, key considerations include: pathogenicity, estimated prevalence among blood donors, the sensitivity and specificity of the proposed tests, the risks of not screening, and the costs of screening in terms of both dollars and impact on blood supply. In the past, prevailing expert opinion and political considerations have also significantly influenced decisions on blood screening, as with both the introduction of hepatitis C and HIV testing.

Dr. Evatt, who was hematologist and director of the Centre for Infectious Diseases at the Centers for Disease Control (CDC) during the HIV crisis, compared the state of scientific knowledge surrounding the HIV test when it was licensed in March 1984 with the scientific knowledge related to vCJD testing currently available in 2009.

- In 1984, there was a reasonably good HIV screening test and an HIV confirmatory test, whereas vCJD screening tests are currently still under development and confirmatory testing has yet to be done.
- In 1984, there was pretty good information on the prevalence of HIV among blood donors, whereas with vCJD there are currently only estimates of prevalence in the population and these vary quite widely depending on the risk assessment model, methods, and parameters used.
- By the end of 1984, there was reasonably certain information that HIV could easily be transmitted in blood, whereas at this point in time, there is still a lack of information on the transmissibility of vCJD through blood.
- There was good information in 1984 on the sensitivity and specificity of the HIV screening test, and researchers are now getting this type of information with the vCJD assays under development.
- At the end of 1984, there was reasonably good information on the ultimate outcome of a positive HIV test, but there is as yet almost no information on the ultimate outcome of a positive test for vCJD.

There are several issues related to the introduction of vCJD screening that need to be addressed:

- There is a good screening test but as yet no confirmatory test.
- There is no known treatment.
- The natural history of vCJD in blood is unknown, making it hard to counsel someone who tests positive.
- Test information goes into medical records and as a result, a patient who tests positive may have trouble getting health insurance and medical treatment may be compromised.
- Lack of information on the risks of vCJD transmission and routes of exposure can lead to social stigmatization and discrimination.

Informed consent and screening, a high degree of accuracy and specificity, correct interpretation of test results, supplemental testing to confirm positive results, and follow-up are critical. Beyond these clinical requirements, the management of the psychological and social issues related to a positive diagnosis must also be addressed. It is vital to provide counselling, follow-up, and medical referral since testing positive can greatly affect people's lives, particularly for those in high-risk groups such as people with hemophilia, he concluded.

vCJD in the U.K.: The Patient's Perspective

CHRIS JAMES, EXECUTIVE DIRECTOR, U.K. HAEMOPHILIA SOCIETY

Chris James gave an overview of recent vCJD developments in the United Kingdom, the impacts on patients, and the measures taken by the Department of Health, Health Protection Agency and U.K. Haemophilia Society to try communicate timely, accurate information on vCJD transmissibility and risks.

In the initial years following the first reported case of vCJD in 1996, the prevailing assumptions regarding vCJD risk were that anyone who ate beef in the U.K. between 1980 and 2001 had a very low but continuing risk of developing the disease, and that patients who received plasma products during this period had just a slightly higher risk. Then in December 2003, the first case of vCJD associated with blood transfusion was identified in the U.K. Following a risk assessment exercise, the U.K. Health Protection Agency announced in mid-2004 that all patients who had been treated with UK-sourced pooled plasma products between 1980 and 2001, an estimated 4,000 to 5,000 people, were now considered at an increased risk of developing vCJD. The agency sent letters to these patients informing them that they may have been given products from implicated batches (manufactured from a plasma pool that contained at least one donation from a person who later developed vCJD) and that due to their potential vCJD infectivity, the patients were to be classified as "at-risk of vCJD for public health purposes." Patients were given the option to find out whether they had been given plasma from an implicated batch; around 200 patients (4 to 5 per cent) wanted to know. Since then, it has become known that 802 patients are in the implicated group.

In December 2008, the U.K. Department of Health announced the discovery of abnormal prions post-mortem in a man with hemophilia and then in February 2009, health authorities updated its risk assessment to indicate that the most likely source of vCJD infection was treatment with UK plasma. Unfortunately, the Haemophilia Society was given very short notice of the impending announcement, finding out from the Department of Health only the day before a story appeared in the national press because the information had been leaked. The health department had a letter ready to be sent to patients through the hemophilia centres. "This raised anxiety within the hemophilia community – from the first letter in 2004, the concern now changed from a very theoretical risk to something that was more real," he said.

The Department of Health investigated the possible routes of infection for this patient and published its full risk assessment in June 2009. The main finding was that although treatment with UK plasma-sourced clotting factors is considered the most likely source of vCJD infection, in this case, the patient's infectivity might not have come from the two implicated batches of clotting factor. The patient had also received several transfusions of red cells and also had undergone surgical procedures in the past. This again caused heightened anxiety, particularly for patients who had received red blood cell transfusions, although there was no actual change to the risk status. U.K. authorities again prepared a letter to update patients on this case. The Haemophilia Society grappled with whether or not to send the letter to its members. In the end, some HTC's sent the letter to their patients, and the Haemophilia Society prepared its own guidance information and posted it on its website.

The impact on patients is that they are, to a lesser or greater extent, actually suffering some discrimination due to being deemed at risk for health purposes, he said. There are reports of patients who keep having their surgeries postponed or cancelled and patients having to purchase their own equipment for medical procedures because of the special safety measure needed for certain types of surgery or investigations. Some patients feel singled out again as a group as happened with HIV and HCV.

The Department of Health has been studying the consequences and implications of screening blood donations for vCJD prions, particularly in terms of health services, public health, and the blood supply. Meanwhile, the U.K. Clinical Governance Advisory Group has recommended resources for at-risk groups to gain access to testing. One concern is that some patients or patients groups might want access to a test with lower specificity than that required. One of the key challenges is the difficulty to assess and explain the meaning of a positive screening test.

Outstanding uncertainties about vCJD testing could cause raised anxiety but it is important to inform the patients as much as possible, he said. Also, research shows that testing may not be emotionally devastating. Provisional results from a qualitative research study in the U.K. on how individuals said to be at risk of prion disease reacted to the notification suggest that most were able to deal with the unwelcome information and continue their lives, he said.

There are a number of important considerations that should be taken into account by health agencies in the planning of vCJD screening programs. These include:

- Ensure that patients who test positive have access to a designated neurologist and the National Prion Centre.
- Provide additional testing for people who test positive and want confirmatory tests (extraction of tonsil tissues, testing for genotype, etc.).

- Deal with issues such as potential refusal of life insurance, employment etc.
- Establish an ongoing vCJD Helpline, with expertise and support provided by the Society or other patient groups.

The U.K. Haemophilia Society's stated position is for any test for vCJD to be brought in as soon as available but with proven efficacy for patients and that counselling to be provided before and after testing, he concluded.

variant Creutzfeldt Jakob Disease vCJD transmission, testing, risk assessments

BRUCE RITCHIE, DIVISION OF HEMATOLOGY, DEPARTMENT OF MEDICINE, UNIVERSITY OF ALBERTA

Introduction of blood screening tests for variant Creutzfeldt Jakob disease is needed to advance vCJD epidemiology, said Bruce Ritchie. In his view, the level of uncertainty about vCJD is very similar to that surrounding AIDS when the HIV test was introduced in 1984. The first case of AIDS in a patient with hemophilia had been reported only the year before so when the HIV test became available, there were the same questions about risk, transmission, prevalence, incidence, and what the results of the test meant. But since these pathogens can have devastating effects, testing is vital to gaining a better understanding of vCJD.

Screening programs need to be carefully planned. The HIV experience has shown the importance of risk communication, testing, and counselling. People need to know and be told about the risks, he said. The Blood Borne Pathogens Surveillance Project in Canada, started in 2000, requires patients who enroll to consent to be informed of their test results; it is currently following 1,664 patients. Surveillance is also important to protect the safety of the blood supply and inform public health planning and policy.

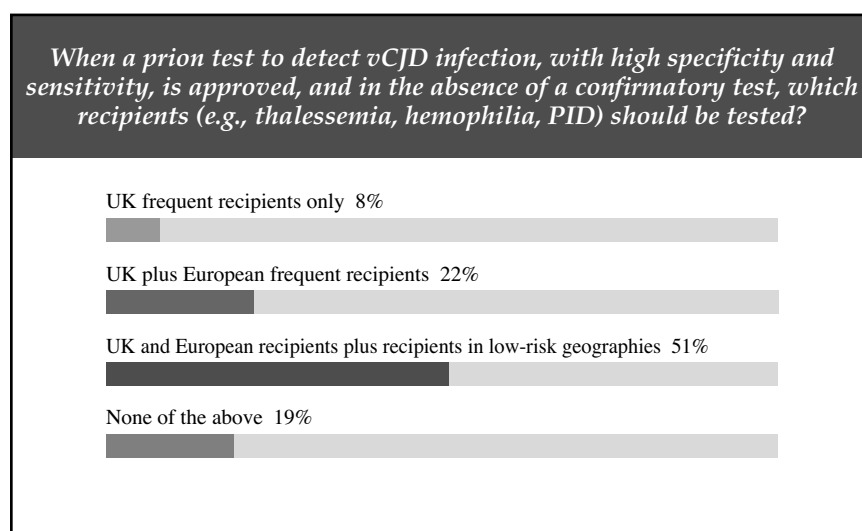
vCJD has implications for people both within and outside the U.K. Testing of both blood donors and recipients is needed to understand transmission risk, which in turn will inform whether blood donor deferral is sensible and which donors to defer. Large-scale testing would be needed to assess the risk in the general population. Testing is also important in order to confirm the clearance of prions during the production process. Finally, testing for vCJD should not be left just to the physicians, clinic staff, or public health authorities—it must be a collaborative approach that includes informed participation of patients and other populations that are to be tested, he concluded.

Discussion

The audience was polled on who should be tested in the event that a vCJD prion test is approved in the absence of a confirmatory test. Chair David Page noted that a slim majority of participants, 51 per cent, were in favour of testing all recipients of treatment with blood products (e.g., thalassemia, hemophilia, PID).

When a prion test to detect vCJD infection, with high specificity and sensitivity, is approved, and in the absence of a confirmatory test, which donors should be tested?

UK donors only	18%
UK donors plus European donors	38%
UK donors plus European donors plus donors in low-risk geographies	32%
None of the above	13%



There is a lot of uncertainty about patients considered at-risk of vCJD for public health purposes—such that at-risk patients who test negative for prions can sometimes still not be considered zero risk, noted Mike Makris of the U.K. To reduce transmission risks, when procedures involving biopsies are performed in patients considered at-risk of vCJD, the surgical instruments used are quarantined; last year, about 14 endoscopes at the Sheffield Hospital were quarantined for this reason, limiting the availability of endoscopes for general use. Following the death of a patient considered at risk of having vCJD, a full autopsy of all brain, lymphoid and tonsil tissues found no vCJD. However, despite the fact that there was no histological evidence of vCJD, U.K. health authorities felt that it was still not sufficient evidence that the patient did not have VCJD and therefore, the endoscope used could not be recirculated for general use, he said.

Nabae Koji of the Japan Ministry of Health noted that different countries have carried out different risk assessments and adopted different donor deferral criteria. “To what extent have the outcomes helped regulatory agencies set donor deferral criteria and how sensible is donor deferral?” he asked. Donor deferral criteria set by regulatory authorities in different parts of the world are ultimately pragmatic decisions focused on maintaining the sufficiency of blood supply, said Albert Farrugia. No donor referral policy has obviated risk, with the possible exception of Australia, which in 2005 initiated a policy restricting the blood donor pool for plasma collected for the production of factor VIII concentrates to people who had not lived or travelled outside Australia and New Zealand (there have been no confirmed cases of BSE or vCJD in either country). This restriction was only possible because the government also increased access to government-funded recombinant factor VIII, he said.

Alok Srivastava asked what gold standard was used to measure the sensitivity and specificity of the Amorfix test in the France study. Dr. Adams explained that the sensitivity was based on spike samples from the U.K. given that there are at this point in time no pre-clinical blood samples from people with vCJD. The specificity study found 20 positive samples out of the 30,000 blood samples but since it was an anonymized study, it was not possible to get additional samples from those who tested positive to perform a confirmatory test to determine if they are real cases or false positives. Dr. Srivastava noted that this is not the classical way to assess specificity and sensitivity.

One of the lessons learned from HIV and HCV is the value of prospective testing, whether according to clinical risk factors or of at-risk or broader populations, said Keith Hoots (USA). As a result, extensive resources have been invested to create bio-repositories in hemophilia and larger disease areas which are not “anonymized” and prospectively obtain biospecimens to allow phenotypic correlation and look-back for positive tests. Prospective studies with the informed consent of participants need to be done to decide this important issue.

Dr. Adams explained that the uncertainty about what to do with a positive result is a key challenge, therefore Amorfix decided to carry out anonymized testing first to get a sense of the extent of vCJD risk before conducting a non-anonymized prospective study, which would give researchers time to try determine what to do with positive test results and possibly develop a confirmatory test.

Session 7: Innovations and Updates

CHAIR: DR. PAULA BOLTON-MAGGS, CONSULTANT HAEMATOLOGIST, MANCHESTER, U.K.

The final session presented some of the innovative research and programs currently going on towards the development of new and better forms of treatment for people with inherited bleeding disorders. The presentations included an overview of challenges in the development and licensing of treatment products for rare bleeding disorders, and different initiatives to develop long-acting recombinant factor products, recombinant factor fusion proteins, and recombinant porcine factor.

Development of New Recombinant Products

DORTHE VIUFF, DEPARTMENT OF MOLECULAR PHARMACOLOGY, NOVO NORDISK

Novo Nordisk has several projects ongoing that aim to improve treatments for people with hemophilia who have developed inhibitors and bring about the next generation of treatments, said Dr. Dorthe Viuff.

Novo Nordisk manufactures a recombinant factor VIIa (rFVIIa) product called NovoSeven® for the treatment of hemophilia patients with inhibitors to factor VIII or IX, and is currently working to develop a subcutaneously administered factor concentrate, long-acting rFVIIa derivative and fast-acting rFVIIa analogue. In addition, research is underway to develop recombinant factor VIII (rFVIII) for patients with hemophilia A, and a recombinant factor IX (rFIX) for patients with hemophilia B. A recombinant factor XIII (rFXIII) for patients with factor XIII deficiency is already in clinical trials,

A key research priority is to develop a long-acting recombinant factor VIII option that would provide improved prophylaxis with a reduced dosing frequency. Novo Nordisk is working on a highly purified third-generation rFVIII product called N8 that is serum- and albumin-free, and in its active form is identical to wild-type FVIII, she said. A five-step purification process is used to minimize risk of viral contamination: detergent inactivation, immunoaffinity chromatography, anion-exchange chromatography, nanofiltration, and gel filtration.

A preclinical study was done to evaluate the in vivo efficacy comparing N8 to Advate®, the rFVIII product manufactured by Baxter. Hemophilia A mice were randomized and dosed blindly intravenously with N8 or Advate® at 1, 5, 20, 50, 100 and 200 IU/kg or placebo, with normal mice included as controls. Bleeding was initiated five minutes after dosing and blood loss and bleeding time were measured for 30 minutes. The hemophilia mouse model exhibited similar dose responses for N8 and Advate®, with a normalization at 200 IU/kg. No differences in efficacy and potency were shown for N8 and Advate® with respect to blood loss and bleeding time.

Novo Nordisk is now conducting an international multi-assay, multi-centre, randomized and blinded study comparing N8 to Advate®. The study consists of a sequence of clinical trials (pharmacokinetic, treatment and prevention and surgery trials in adults and then in children) based on FDA and EMEA requirements on recombinant factor VIII products. There are 33 laboratories worldwide participating in the study.

Fusion Protein Technology – Potential Treatment for Hemophilia

DR. GLENN PIERCE, VICE PRESIDENT AND CHIEF MEDICAL OFFICER, BIOGEN IDEC

Fusion protein technology using the neonatal Fc receptor (FcRn) to transport factor VIII and IX proteins is showing strong potential as way to advance the treatment of hemophilia, said Dr. Glenn Pierce. He described progress to date by Biogen Idec, in collaboration with Biovitrium, on the development of long-acting recombinant factor products.

The FcRn protein is found in the endothelial cells of blood vessels and has been demonstrated to be responsible for the extended circulation and plasma half-life of the immunoglobulin G (IgG) antibodies. Upon binding to the FcRn, the IgG molecule is taken into the endothelial cells and then recycled into circulation, rather than taken out of the bloodstream. Thus FcRn protects IgG from degradation and keeps it in circulation longer such that the half-life of IgG is generally several weeks. Fusion protein technology is a well-established approach to improving half-life for a range of effector molecules. Numerous recombinant Fc fusion proteins have been approved for clinical use in autoimmune diseases such as rheumatoid arthritis, chronic psoriasis, and immune idiopathic thrombocytopenic purpura.

Traditional Fc fusion proteins are dimeric, whereas Biogen Idec has developed proprietary monomeric Fc fusion technology that is being applied to improve the pharmacokinetic and pharmacodynamic properties of recombinant factor concentrates. Monomeric Fc fusion proteins appear to be more efficiently recycled than traditional dimeric Fc fusion proteins, and therefore demonstrate a longer half life in this novel configuration. Factor products with a longer half-life would reduce the dosing frequency required to maintain prophylaxis and thereby lead to improved management of hemophilia, particularly the challenge of inhibitors.

Preclinical pharmacokinetic studies of the recombinant factor IX Fc fusion protein (rFIXFc) in a variety of animal models demonstrated a three- to fourfold increase in half-life compared to a recombinant factor IX product (Benefix®). Phase I/IIa pharmacokinetics studies on rFIXFc carried out in the United States and other countries were near completion, and transition to a global pre-licensure study will soon be underway.

The preclinical data on the recombinant factor VIII fusion protein (rFVIIIc) shows specific activity and half-life comparable to existing factor VIII products. The first in-human study for rFVIIIc will begin shortly (Phase I/IIa pharmacokinetics studies) and would be followed by integrated licensure study.

“Moving forward, our goal is to assess safety and efficacy of this technology and evaluate its potential to increase the half-life of recombinant factors, and really impact the treatment and prevention of bleeding in patients with hemophilia,” Dr. Pierce concluded.

Recombinant Porcine Factor VIII: Promising Treatment for Patients with Inhibitors

JEFFREY LAWRENCE, SENIOR DIRECTOR OF MEDICAL DEVELOPMENT, HEMATOLOGY, IPSEN

The development of recombinant porcine factor VIII (OBI-1) by Ipsen continues to advance and show promise for new treatment for hemophilia A patients with inhibitors, said Jeffrey Lawrence. He presented data from the Phase II trial on OBI-1 and described plans for the Phase III trial that will soon get underway.

Current data suggest that hemostasis in inhibitor patients who no longer respond to human factor VIII therapy (25 to 30 per cent of patients with severe hemophilia A and 3 to 13 per cent patients with mild and moderate hemophilia A) is typically initiated via the extrinsic/tissue factor pathway through frequent doses of activated factor VII (FVIIa) or activated prothrombin complex concentrate (APCC), Dr. Lawrence said. "However, this requires tremendous amounts of thrombin to initiate fibrinogen, platelets and other components of the coagulation cascade. Importantly, factor VIII and factor IX need to be involved—generally about 90 per cent of thrombin is generated through the factor VIII- and factor IX-dependent intrinsic pathway. Recombinant porcine factor VIII has exciting potential to address hemostasis through the intrinsic coagulation pathway."

Another important clinical benefit of recombinant porcine factor VIII is the ability to monitor and dose patients. With rVIIa and APCC there are no monitoring tests that can be used to select dose or monitor effectiveness of therapy; studies on effectiveness and optimum dosing, whereas a factor VIII product permits dosing in non-inhibitor patients with hemophilia A to initially look at the recovery of the treatment and then over the course of therapy monitor the achievement of hemostatic factor VIII levels, he said. "This is a strong advantage of recombinant porcine factor VIII for these difficult to manage inhibitor patients."

OBI-1 is a B-domain deleted recombinant protein that is 94 per cent homologous with human factor VIII and studies show that it has equivalent coagulant function. Preclinical and Phase I and II clinical studies suggest that porcine factor VIII has low cross-reactivity with human factor VIII inhibitors; it is expected that factor VIII inhibitors will not neutralize OBI-1 and therefore it will be possible to manage patients as if they did not have an inhibitor, using the intrinsic pathway, just as for treating patients with hemophilia A who do not have inhibitors.

The Phase II trial to assess the hemostatic activity of OBI-1 in congenital hemophilia A patients with inhibitors and non-life or -limb threatening bleeding episodes involved 9 patients who together had 25 bleeding episodes, and demonstrated 100 per cent efficacy. All bleeds were successfully controlled with 8 or fewer injections of OBI 1 (median total dose 224 U/kg), and 20 of the 25 bleeds (80 per cent) were controlled with a single treatment dose of OBI-1 (median total dose of 201 U/kg). While 8 of the 9 patients who received multiple injections exhibited an elevation of titer against OBI-1, there was no drop in efficacy in terms of the number injections required to control the bleeding, Dr. Lawrence reported. In addition, there was no increase in the incidence of adverse effects with repeated exposure; one patient had a mild adverse infusion reaction that was controlled with diphenhydramine but when later treated for a subsequent bleed did not have any adverse effects.

Ipsen is now planning two parallel Phase III clinical trials to examine the safety, efficacy and pharmacokinetics of OBI-1 in the treatment of severe and life-threatening bleeds in patients with congenital hemophilia A with inhibitors, and the treatment of acute bleeding episodes in patients with acquired hemophilia A. These will be open-label, non-comparative prospective studies; the target enrolment is 40 patients in each study. Beyond assessing the efficacy and safety of OBI-1, the researchers also plan to collect pharmacogenomic and other immunological studies that will hopefully advance the state of the art and the understanding of the natural history of congenital hemophilia A with inhibitors and acquired hemophilia A. As there have been no prospective studies done in either of these populations with any agent, there are a number of clinical challenges with regard to site identification and patient management; experts in the field have provided input on how to address this and clinicians and centres were encouraged to enroll their patients. Ipsen expects to initiate Phase III activities early in the year 2010.

Rare Bleeding Disorders: The Challenges

DR. CLIVE DASH, BIO PRODUCTS LABORATORY (BPL)

Bio Products Laboratory (BPL) is a division of the Blood and Transplant Authority of the United Kingdom National Health Service and manufacturer of high-purity plasma-derived products that are distributed worldwide. Dr. Clive Dash gave an overview of the steps and challenges involved in BPL's development and licensing of a high-purity plasma-derived factor X concentrate for the treatment of factor X deficiency.

Extensive planning and international market research was invested to identify the patient population and therapeutic needs, and build the business case for developing the new treatment product. This involved gathering clinical information on disease prevalence and patient phenotypes, and important considerations such as protein purification and yield, the impact on licensed products downstream in the fractionation process, cost of manufacturing, and orphan drug designation criteria.

Key challenges included identifying suitable patients and centres with potentially suitable patients, correlating the market research with reality, meeting regulatory requirements for clinical studies given the small subset of target patients, setting up properly validated assays, and encouraging clinicians with only one or two patients that it is worthwhile to take on the administrative burdens associated with clinical trials.

Orphan drug status in Europe and the United States was obtained and BPL subsequently applied for parallel protocol assistance and advice from EMEA and FDA. A single protocol was submitted for joint review by the regulatory bodies, which was followed by separate discussions with each agency. Given the different requirements of the two agencies, the licensing dates in the U.S. and Europe may also differ. The process presented opportunities to gain a better understanding of the different regulatory approaches and conducting clinical trials abroad in compliance with good clinical practice, and work with clinicians who are particularly interested in a rare bleeding disorder.

Overall, developing a product for a rare bleeding disorder can require a longer planning and development cycle compared to products for more common medical conditions, he said. And while the product license application may possibly require slightly less data, the cost of clinical trials is not reduced, though there are some financial benefits for sponsors of orphan drug designation as some of the regulatory fees are reduced or annulled, he concluded.

Advancing Factor Replacement Therapies for Rare Bleeding Disorders

LUTZ BONACKER, GLOBAL HEAD, COAGULATION THERAPEUTICS, CSL BEHRING

CSL Behring produces a number of plasma-derived and recombinant factor replacement products for the treatment of rare bleeding disorders. Dr. Lutz Bonacker described several factor products in the CSL Behring global pipeline, at different stages of research and development, licensing and marketing worldwide.

CSL Behring's factor I/fibrinogen concentrate for the treatment of congenital fibrinogen deficiency was introduced in Germany in 1986 under the trade name Haemocomplettan® and is currently marketed in an additional 12 countries. In January 2009, licensing under the trade name Riastap® was approved in the United States and a clinical trial is underway to assess its efficacy and safety in treating acute bleeding episodes in patients with

congenital fibrinogen deficiency. Future activities will explore the use of fibrinogen concentrate as prophylaxis to prevent bleeds and before surgical interventions. CSL Behring also has two ongoing trials in the United States towards obtaining marketing authorization for its prothrombin complex concentrate product Beriplex® P/N, first licensed in Germany in 1996 and now licensed in 18 additional countries for the treatment of congenital or acquired deficiency of clotting factors II, VII, IX, and X.

Dr. Bonacker also presented data on CSL Behring's ongoing development of recombinant factor IX fusion proteins (rFIX-FP) using albumin fusion technology to extend the half-life of factor IX products. Albumin is a highly abundant protein with a long half-life of approximately 20 days. Albumin fusion technology holds promise as a way to deliver longer-acting therapy to patients with hemophilia B who have inhibitors. Albumin is fused to the C-terminus of FIX; the rFIX-FP contains a cleavable linker between the factor and albumin derived from FIX activation region.

In vitro and in vivo studies of rFIX-FP containing a cleavable linker demonstrated a five- to tenfold increase in clotting activity of rIX-FP over a rFIX-FP with non-cleavable linker, and a two- to fourfold extension of terminal half-life over wild-type rFIX in rats, rabbits and dogs. rFIX-FP was also found to have significantly increased in vivo recovery over wild-type rFIX, and equivalent efficacy. These results indicate the potential of rFIX-FP as a coagulation product that would require less frequent infusions to achieve the same therapeutic effect. CSL Behring continues to its investigation and development this recombinant fusion protein towards improving therapy for patients with inhibitors.

Discussion

There is good evidence to suggest that the pharmacokinetic profile of medications in children is generally shorter than in adults, but very little data on the pharmacokinetic parameters in children, said Victor Blanchette. However, this data is more available in adults, where pharmacokinetics in adult patients who are outside the inhibitor range typically stays stable over an interval of one month or so. As the various pre-licensure and pharmacokinetic studies are planned, some consideration should be given to how to get that type of data on children, which would be useful.

Chair Paula Bolton-Maggs remarked that it has been very encouraging to see the developments going on related to different therapies and the different technologies that being used. Following on the discussions about the challenges facing the bleeding disorders community, it is good to be able to look forward to some very significant advances in treat that will hopefully translate into benefits for our patients, she said.

Closing Remarks

WFH president Mark W. Skinner thanked all the speakers and participants for sharing their expertise and perspectives over the course of the global forum, and recapped some of the common themes and key discussions over the past two days.

Throughout the conference, participants emphasized the importance of robust data and evidence to support the ongoing work to advance hemophilia care and provide a foundation for confronting emerging challenges. Jeffrey Stonebraker presented new research on worldwide factor VIII use from 1996 to 2006 that showed the significant progress and steady increases in per capita factor VIII use across most of the countries surveyed. These research findings will serve as a very useful tool for future product development and for healthcare planning in different countries around the world. Patrick Robert presented several forecasts on global trends, changes, and needs related to plasma in the next years, describing the narrowing gap between industrialized and developing countries in terms of product availability.

A comparison of different approaches to prophylaxis demonstrated that while there has been great progress made in optimizing preventative therapy regimens and their outcomes, a lot of vigorous research continues around the world. Kathelijn Fischer described the Van Creveld prophylaxis protocol and studies comparing the Dutch and Swedish regimens and their patient outcomes, while Victor Blanchette presented data from the ongoing Canadian prophylaxis study on dose escalation. Alok Srivastava described a new low-dose prophylaxis approach being explored in developing countries. Key questions that still need further investigation include: when to start and when to stop prophylaxis, which approach is best, and whether it is actually possible to bring about the levels of treatment that exist today in developed countries to developing countries with very little resources.

The session on health technology assessment and comparative effectiveness research served as a wake-up call for the global bleeding disorders community on possible threats to hemophilia care in the coming years as governments confront rising fiscal deficits and social expenditures. Michael Lauer emphasized the need to gather both scientific and qualitative evidence on hemophilia treatment, and Adam Hutchings stressed that clinicians and patient organizations must get informed about any potential changes to healthcare funding that could affect hemophilia and get involved in the discussions and assessments. Collaboration among all the different stakeholders will be very important to face the looming threats and find solutions to ensure that hemophilia care is protected and sustained.

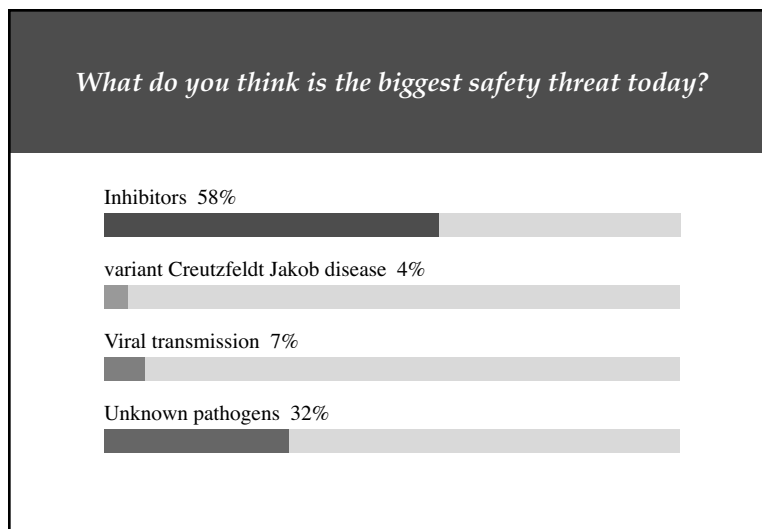
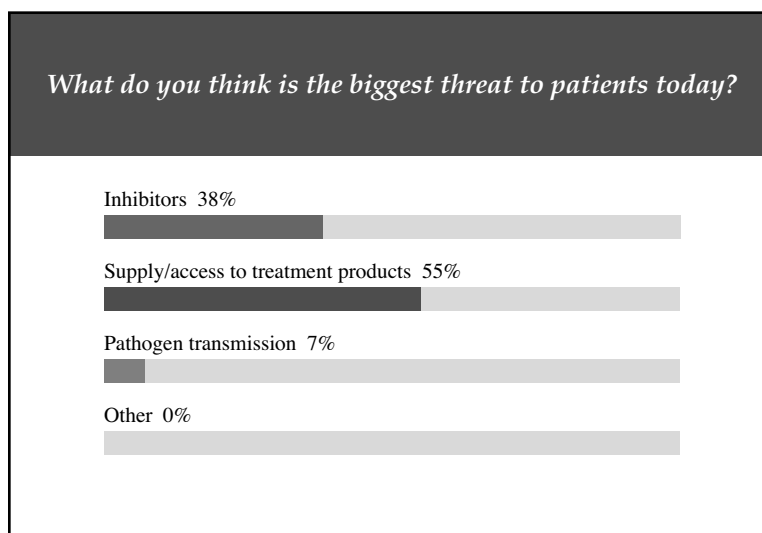
Then the biosimilars session examined the potential benefits and risks of these types of products, and how to help enter the market more easily and more perhaps cost effectively. The audience poll to assess participant perceptions, while not definitively conclusive, showed that more than 70 per cent felt that biosimilars hold hopeful potential for the bleeding disorders community but there are still safety issues that must be considered moving forward.

The session on inhibitors featured case studies from around the world and showed very clearly that global collaboration and harmonization in terms of both data collection and laboratory technologies is critically needed. Dr. Alison Street, WFH VP Medical, underscored the WFH's commitment to advance inhibitors research and to lead or facilitate initiatives towards international data harmonization.

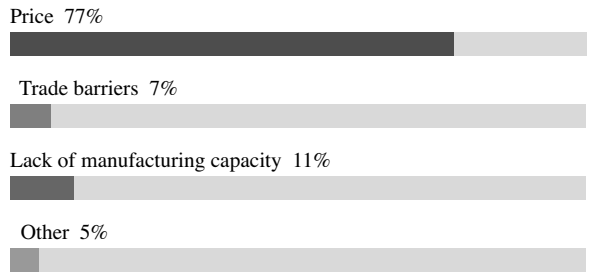
The session on variant Creutzfeldt Jakob disease, an ever-present concern, provided a comprehensive look at vCJD transmission risks, testing, and some of the implications of screening for people with bleeding disorders as well as blood product safety and supply. The audience poll indicated that there is a perception that testing is ultimately good and that perhaps patients around the world should have access to testing, but there are a number of important issues such as pre- and post-test counselling and proper governance of testing that are critically important to success.

The final session gave a sampling of some of the innovative programs and research initiatives going on with novel therapies, including the exciting progress in the development of new technologies to enhance factor VIII products and of new products for other rare bleeding disorders such as the factor I, X and XIII deficiencies.

Mr. Skinner again thanked everyone for their participation and looked forward to seeing them at the next global forum.



What do you think is the biggest supply threat today?



Glossary and Acronyms

Bernard-Soulier syndrome: A severe congenital bleeding disorder characterized by thrombocytopenia and large platelets, due to a defect in the platelet glycoprotein 1b/V/IX receptor.

BSE: bovine spongiform encephalopathy

CDC: United States Centers for Disease Control and Prevention

CER: Comparative Effectiveness Research

CFC: Clotting Factor Concentrate

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

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.

Desmopressin (DDAVP): A synthetic hormone used to treat most cases of von Willebrand disease and mild hemophilia A. It is administered intravenously by subcutaneous injection or by intranasal spray.

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.

EHC: European Haemophilia Consortium

EMA: European Medicines Evaluation Agency

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.

Factor concentrates: These are fractionated, freeze-dried preparations of individual clotting factors or groups of factors derived from donated blood.

FDA: United States Food and Drug Administration

Finished product testing: Testing done on final product to allow manufacturers to characterize their products and to demonstrate compliance of every batch with the licensed specification.

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

Glossary and Acronyms

Glanzmann's thrombasthenia: A severe congenital bleeding disorder in which the platelets lack glycoprotein Iib/IIIa, the blood platelet count is normal, but their function is very abnormal.

Good manufacturing practices (GMPs): All the elements in established practice that will collectively lead to final products that consistently meet expected requirements as reflected in product specification. These include traceability, segregation of product manufacturing steps to avoid cross-contamination, training, documentation, change control, and deviation reporting.

Hemophilia A: A condition resulting from factor VIII deficiency, also known as classical hemophilia.

Hemophilia B: A condition resulting from factor IX deficiency, also known as Christmas disease.

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

HIV: Human immunodeficiency virus. The virus that causes AIDS

Home care: The patient administers treatment product himself/herself in his/her own home.

HTA: Health Technology Assessment

Identified person: A living person known to have hemophilia, von Willebrand disease, or another bleeding disorder.

Inhibitors: A PWH has inhibitors when their body's immune system attacks the molecules in factor concentrate, rendering it ineffective.

International Unit (IU): A standardized measurement of the amount of factor VIII or IX contained in a vial. Usually marked on vials as 250 IU, 500 IU, or 1000 IU.

Inventory hold: The retention in storage of plasma for fractionation while processes designed to assure donor safety are undertaken.

IPFA: International Plasma Fractionation Association. (The organization for not-for-profit manufacturers of clotting factor concentrates.)

Limit testing: Testing of the plasma pool using nucleic acid testing (NAT) in which a maximum level of viral contamination, rather than an absolute elimination, is the aim.

Lyophilization: The process of isolating a solid substance from solution by freezing the solution and evaporating the ice under vacuum. Freeze-drying.

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

Glossary and Acronyms

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.

Minipools: 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 to 5 % of normal activity in the bloodstream.

NAT: Nucleic acid testing

Nanofiltration: A process whereby protein solutions are passed over small pore filters which can remove viruses while allowing therapeutic proteins to pass through.

NIH: United States National Institutes for Health

NMO: National Member Organization (Of the WFH)

NORD: National Organization for Rare Disorders

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, thus allowing detection of a virus which may cause disease before the development of immunological markers of infection.

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 master file: A dossier of information compiled according to European guidelines, which allows the manufacturer of plasma derivatives to fully describe the source material.

Plasma pool: Plasma from a number of donors used to make one lot of product.

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 donor's plasma is removed. This method allows a donor to donate a larger volume of plasma per donation and donate more frequently than is possible when donating whole blood.

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

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

Glossary and Acronyms

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

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

PWH: Person with Hemophilia.

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

Recombinant products: Factor concentrates that contain factor VIII or IX that have been artificially produced and are, 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.

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

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

Shelf life: The period of time during which a product may be stored under specified conditions and retain its characteristics.

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.

TSE: transmissible spongiform encephalopathy

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.

vCJD: variant Creutzfeldt Jakob Disease

von Willebrand disease: An inherited bleeding disorder resulting from a defect or deficiency of von Willebrand factor.

vWD: von Willebrand disease

WHO: World Health Organization

Window period: The period between when a 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. With nucleic acid testing (NAT), the window period is shortened.



The World Federation of Hemophilia wishes to thank the sponsors of this event:

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