THE EIGHTH WFH GLOBAL FORUM

MONTREAL, CANADA
SEPTEMBER 26-27, 2013

PROCEEDINGS

WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL
WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

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

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8TH WFH GLOBAL FORUM ON THE SAFETY AND SUPPLY OF TREATMENT PRODUCTS FOR BLEEDING DISORDERS

Montreal, Canada
September 26-27, 2013

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The World Federation of Hemophilia gratefully acknowledges the sponsors of the 2013 WFH Global Forum:

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EXECUTIVE SUMMARY

Introduction

The 8th WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders, held September 26-27, 2013, in Montreal, Canada, focused on current issues and developments related to the safety and sustainability of plasma products, clinical and economic aspects of novel treatment products for hemophilia and other inherited bleeding disorders, product choice, and the impact of regulatory factors on product access. More than 120 people from around the world attended this Global Forum, including leading hematologists and clinicians, multidisciplinary health professionals, patient organization representatives, blood services officials, and industry experts. The objectives were to present the latest knowledge and encourage discussion, consensus building, and networking towards addressing global challenges related to treatment safety, supply, and access.

The meeting also highlighted the ever-present issue of access to safe treatment in developing countries. "About 75% of people in the world who have bleeding disorders are not diagnosed and are without access to proper care," noted John Bournas, WFH CEO and Executive Director. At this Global Forum, the WFH officially launched Project Recovery, a groundbreaking initiative in partnership with Canadian Blood Services and plasma product manufacturers Biotest AG and Grifols, which will turn unused blood components from Canadian blood donations into medicines for people with hemophilia in developing countries with little or no access to life- and limb-saving treatment. In addition, the WFH's Close the Gap Campaign is underway to raise funds for the development of sustainable care in areas of the world with the greatest need. To inspire support, WFH patron Jan Willem André de la Porte committed to match and double all contributions made during this Global Forum.

The global bleeding disorders community is on the cusp of great change which will revolutionize treatment and care. New treatment products are about to enter the market as soon as early 2014, and will change the landscape and management of care for people with inherited bleeding disorders. Longer-acting factor concentrates based on new strategies such as pegylation, fusion technologies, and amino acid modification will offer substantially enhanced efficacy and extended half-life. This 8th WFH Global Forum explored the implications of the new therapies in terms of treatment, clinical practice, product choice, and product access, and regulatory requirements and challenges related to orphan drug designation, market exclusivity, and marketing authorization of biosimilars.

The Safety and Sustainability of Plasma Products

David Page of the WFH Treatment Product Safety, Supply and Access Committee opened the first session with a retrospective overview of the WFH Global Forum. First held in Montreal in 2000, the Global Forum has become an important meeting for scientific exchange and international dialogue on important issues related to treatment, blood safety, supply, and access globally. Over the years, the Global Forum has focused on topics such as the global disparities in factor availability and factor consumption, lack of diagnosis and access to treatment in the developing world, blood safety issues such as pathogen transmission, risk of inhibitor development, health technology assessments, clinical and regulatory aspects of biosimilars, and gene therapy research. This meeting would focus on the next generation of factor products and important considerations for the global bleeding disorders community moving forward.

Dr. Thomas Kreil of Baxter BioScience described the "blood safety tripod" of donor selection, testing of blood donations, and virus reduction. There are important distinctions between blood and plasma-derived products. For blood transfusion products, rigorous testing of donated blood is crucial. For plasma-derived products, virus inactivation during the manufacturing process is a critical safeguard. Nucleic acid testing is currently performed for screening and detection of HIV and hepatitis A, B, and C. He described several new viral detection technologies (multiplex polymerase chain reaction, protein and nucleic acids arrays, and massive parallel sequencing) and their potential applications in the field of bleeding disorders.

Dr. Michael Soucie of the Centers for Disease Control and Prevention gave an overview of parvovirus B19 and hepatitis E, evidence of transmissibility, and current prevention strategies. Ongoing surveillance is highly important to ensure continued product safety and detect emerging threats to the blood supply. Effective viral inactivation and detection processes are key defenses to protect recipients of blood products from new or emerging viruses. Dr. Johannes Blümel of the Germany's Paul Erhlich Institute described viral inactivation of non-enveloped viruses, focusing on the hepatitis A virus, hepatitis E virus, parvovirus B19, and parvovirus 4. Viral reduction methodologies such as liquid pasteurization, dry heat treatment, virus filtration, and pathogen inactivation range in effectiveness for different viruses.

David Page then presented the WFH's Project Recovery, a humanitarian aid initiative to transform unused cryoprecipitate from the developed world into safe factor concentrates for the developing world. The project was conceived by the Canadian Hemophilia Society and discussed at the first Global Forum in 2000; its realization follows many years of effort and determination by WFH staff and volunteers, and a number of different partners. It is estimated that in 2014, Project Recovery will provide 5 million international units (IUs) of factor VIII concentrate to the WFH Humanitarian Aid Program, which distributes medicines to developing countries. Ian Mumford, Chief Operating Officer of Canadian Blood Services, spoke about the blood agency's commitment to seeing the project through the technical and regulatory challenges and other complications along the way. Svenja Barckhausen, Director of Plasma Procurement at Biotest, described the company's investment of clinical research and initial costs. Dr. Alok Srivastava, WFH Vice President Medical, spoke about the great need for these life-saving medicines in developing countries. Project Recovery epitomizes the WFH's mission of Treatment for All and will allow the organization to augment and better plan its humanitarian aid donations and distribution, WFH President Alain Weill said.

A debate on the future of plasma-derived products addressed challenges and opportunities for the global plasma industry as new recombinant factor products enter the market. Dr. Magdy El Ekiaby, WFH Vice President Communications and Public Policy, noted that plasma is a raw material and its collection is complex. Plasma for fractionation is currently largely collected from developed countries. A lot of work would need to be done establish blood collection and fractionation infrastructure in developing countries; donations would need to be tested and processed according to international standards and regulatory requirements. The new generation of technologies may well come to prevail in the next two decades as safer, permanent alternatives to plasma products. Dr. Pierre-François Falcou of LFB Biomédicaments countered that the global plasma market is substantial and worldwide demand continues to increase. In recent years, major plasma manufacturers have expanded their fractionation capacities and increased production volumes. Several types of fractionated products are currently driving the plasma industry: albumin, intravenous immunoglobulin (IVIG), and factor concentrates, among others. While it is true that recombinant products, biosimilars, and gene therapy will affect the global plasma market, these active proteins have specificities that the recombinant industry may find difficult to change or reproduce.

Clinical and Economic Aspects of Novel Treatment Products

This session explored current trends related to clinical practice and the continual aim to improve treatment efficacy and health outcomes for patients with hemophilia and other bleeding disorders. Dr. Marilyn Manco-Johnson of the The Children's Hospital Hemophilia and Thrombosis Center in Denver, USA, presented some recent studies which showed the limitations of the annualized bleed rate in managing hemophilia, due to subclinical bleeding which causes incipient joint damage. The annualized bleed rate is unquestionably important. Numerous studies have shown evidence relating the annualized bleeding rate to hemophilic arthropathy. However, the evidence also suggests that clinical joint bleeds in the annualized bleed rate account for only some of the structural joint damage detected by MRI in patients with severe hemophilia. The data also shows the beneficial role of early prophylaxis in the prevention of joint bleeding and hemophilic arthropathy.

Dr. Steven Pipe of the University of Michigan C.S. Mott Children's Hospital, Ann Arbor, USA, spoke about the long-acting factor therapies about to enter the market and the potential for improved and individualized care through new treatment paradigms based on pharmacokinetics. For many years, the goal of prophylaxis has been to maintain a baseline factor level (trough level) above 1% to prevent bleeding into joints, one of the main complications of hemophilia. Current debate focuses on whether a 1% trough level is sufficient to prevent bleeding, and whether higher trough levels are actually needed to achieve the absence of bleeds. A recent study at the Van Creveld Clinic in the Netherlands showed that absence of joint bleeding in hemophilia A might only be reached with a factor VIII (FVIII) trough level of 15%. In practice, there will be varying targets and different reasons why specific approaches are adopted for individual patients.

Dr. Albert Farrugia of the Plasma Protein Therapeutics Association addressed economic considerations of hemophilia treatment including increased supply, cost-effectiveness, and pricing. The supply and consumption of FVIII products over the past 20 years has increased steadily. In 2010, about 3 billion IUs of plasma-derived FVIII products were consumed globally. With more types of factor products and increased supply coming to the market, there is now much greater potential for factor production from both plasma-derived and recombinant sources. While prices are high, there has nonetheless been a steady decline, and prices can be expected to drop further as demand and consumption continue to rise. Dr. Farrugia's pharmacoeconomic study of the cost-effectiveness of prophylaxis compared to on-demand treatment for severe hemophilia A, which examined data from the United Kingdom, United States, and Sweden, has found prophylaxis to be superior in terms of both cost and effectiveness, and within the acceptable range of affordability for healthcare reimbursement in developed countries.

Mark W. Skinner, WFH Past President (2004-2012), focused on the rise of the patient voice and the critical importance of patient engagement, patient-centred care, and shared decision-making in clinical development and health care. The new long-acting factor products entering the market provide an opportunity to rethink target trough levels in hemophilia treatment. The Dutch finding that a 15% trough level actually achieves the absence of joint bleeding, in essence a functional cure, provides a specific target trough level to move towards in order to improve outcomes and further normalize the lives of people with hemophilia. "Economics should not limit our treatment goals. It may be a pragmatic reality to contend with but from a scientific standpoint we need to establish what is needed, correct and appropriate, and what patients value and seek in treatment, and then set about figuring out how to pay for it," Mr. Skinner said. Ultimately, individual patients will have different preferences and circumstances, therefore, personalized treatment will be the cornerstone of hemophilia care in the coming years.

Product Choice

There are rapid developments in the world of bleeding disorders treatment and major changes to come as numerous new products enter the market. A number of novel recombinant products will join the many plasma-derived and recombinant products that currently exist. Still, there will be an ongoing demand for plasma-derived products in developing countries where affordable treatment products are often in short supply or non-existent. To set the framework for a plenary discussion, four panelists shared different perspectives based on their experiences in the regulatory, industry, clinical, and patient advocacy fields.

Albert Farrugia of the Plasma Proteins and Therapeutics Association said clinicians must have the clinical freedom to use the treatment products that are most appropriate for their patients; they should not be limited by strategies imposed by health authorities based solely on lowest price. Some countries with mechanisms such as national tenders and procurement schemes have managed to produce a product choice landscape with a multiplicity of players and competitive pricing. It is dangerous to let a single player or monopoly dominate the market. The multiplicity of players and products entering the market will be beneficial for the global bleeding disorders community, and will hopefully also be accompanied by rising demand and supply.

Brian O'Mahony, Chair of the WFH Treatment Product Safety, Supply and Access Committee, highlighted some concerns related to biosimilar or therapeutically equivalent products. There are small differences which need to be carefully analysed and considered. Under European Union law, selection of treatment products can be made based on price or the most economically advantageous tender. "Cost is always a high factor in the decision but it is a major mistake to not look at safety, efficacy, quality, availability of supply, scientific support, and the other factors," he cautioned. Vigilance, knowledge, and full involvement of physicians and patient representatives in the tender selection process are critical. In some countries, physicians and patient organizations are fully involved in every step of the tender process and participate on advisory committees to advise the Ministry of Health on product criteria and choices.

Dr. Nigel Key, WFH Vice President Programs, described the U.S. payer system and some limitations to product choice in different contexts. He strongly advocated for patients and physicians working together to ensure access to product choice. In the U.S. healthcare system, middleman mark-ups affect price—it is not always necessarily the manufacturer price but rather the price charged to the third-party payer that can be tremendously high. National tenders can help drive down price.

Dr. Margareth Ozelo, Director of the International Hemophilia Training Centre at the University of Campinas in São Paolo, Brazil, described the increasing availability of hemophilia treatment in the country over the past two decades. For many years, physicians did not have the option to choose a specific product for patients. The centre generally had different brands of plasma-derived products at any given time and physicians used whatever product was available. In 2003, Brazil introduced a tender system for the purchase of treatment products. Products are selected on the basis of lowest price, with parameters set out by clinical experts and patient leaders. Since then, the government has gradually increased the budget for hemophilia care, treatment parameters have expanded, and patients now have access to recombinant products for bleeding disorders.

Impact of Regulatory Factors on Product Access

This session focused on the impacts of regulatory policies on clinical development and access to bleeding disorder treatment products around the world, and implications for clinical practice. Over the past two decades, regulatory authorities around the world have introduced legislation to stimulate the development of drugs for rare diseases, called orphan drugs, with incentives such as market exclusivity, tax credits, and research support. Dr. Flora Peyvandi, Director of the Angelo Bianchi Bonomi Hemophilia and Thrombosis Center in Italy, described some challenges related to the new long-acting factor products. Hemophilia meets the conditions for orphan disease designation, and these new products could qualify as orphan drugs and benefit through a period of market exclusivity. However, market exclusivity could potentially create a monopoly and hinder market competition, which is important to ensuring the widest possible access and most affordable prices. A particular concern in Europe is the regulatory requirement for pediatric clinical studies, which means that European market authorization for the new products will likely occur two to three years after the products become available in the United States, that is, after prices are already established.

Dr. Jerry Powell, Director of the Hemostasis and Thrombosis Center of University of California at Davis, USA, said moving forward with the novel treatment products, it is important to address several concerns: half-life considerations, adverse side effects, and risk of inhibitor development. Frequency of dosing is determined by factor half-life, deemed to be 10 hours for currently available FVIII products; however, individual variations range from 6 to 16 hours. According to results from clinical studies, the new factor products, depending on the mechanism and on individual patients, provide a 1.5 to 1.8 mean increase in half-life, with individual half-life ranging from 7 to 32 hours. Clinicians need to have the flexibility to study the new products after marketing in order to determine which product will provide the maximum benefits and advantages for each patient, he said.

Dr. Marijke van den Berg of the University Hospital of Utrecht in the Netherlands gave an overview of the evolving safety paradigm for blood products, concerns related to immunogenicity and product switching, and considerations for the clinical development and use of the new long-acting products and biosimilars. The new factor products will offer improved biosynthesis and prolonged half-life. The products fit the definition and criteria for biosimilars. However, while a new biosimilar product may be based on the same techniques, cell systems, cell lines, and processes of a previous product, there are still large knowledge gaps. Biosimilars must demonstrate the same safety profile to be interchangeable. Comparable clinical data is needed but it will be very difficult to collect the data given the growing competition and number of new extended half-life and biosimilar products entering the market, and small patient populations. The right balance between safety and feasibility is needed.

Research and Development Pipeline

Scientists continue to advance innovative research and development of new and improved products for the treatment of hemophilia and other rare bleeding disorders. In this session, representatives from four pharmaceutical manufacturers presented their latest research and updates.

Pam Foulds, Senior Director of Global Medical Affairs Hemophilia at Biogen Idec, presented pivotal data on their long-acting recombinant FVIII Fc fusion protein and recombinant FIX Fc fusion protein. Phase III studies on safety, efficacy, and pharmacokinetics have been completed and Biogen Idec has filed biologics license applications in the United States, Canada, Australia, and Japan. Robert Peters, Senior Director of Hemophilia Research, described future possibilities for FVIII half-life extension. In addition to Fc fusion technology, there are several long-acting FVIII therapies based on pegylation technologies currently being assessed in clinical trials. Phase I and IIa study results show that these

therapies all have greater half-life of about 1.6 times and will make a significant clinical difference in the management of hemophilia A.

Dr. Armin Reininger, Head of Global Medical Affairs Hemophilia at Baxter Innovations, presented data from prospective clinical studies on prophylaxis which show a wide variance in factor use in patients on pharmacokinetic-tailored prophylaxis to maintain at least 1% trough levels. He outlined a framework for tailored therapy based on individual trough levels and annual bleeding rates.

Knud Vad described Novo Nordisk's new recombinant FVIII product based on advanced protein and purification technology and designed for reliability, safety, and portability. The product has demonstrated good efficacy in bleed prevention and treatment, and no inhibitor development in Phase III trials of previously treated adults and children with severe hemophilia A. Novo Nordisk has filed marketing authorization applications in Europe, the United States, Japan, and Switzerland. Final marketing authorization in Europe and the United States is anticipated in the coming months.

Mathias Juers, Director of Medical Affairs and Commercial Development Coagulation at CSL Behring, described the company's ongoing development of new recombinant factor therapies which aim to confer extended half-life, lower immunogenicity, and reduced bleeding frequency. Products in the pipeline include recombinant single-chain FVIII and recombinant FIX, FVIIa, and VWF fusion proteins. CSL Behring's plasma-derived FVIII/VWF concentrate was granted marketing authorization by the European Medicines Agency earlier this year.

Key Points from the 8th WFH Global Forum

The World Federation of Hemophilia's work in the area of treatment safety, supply, and access has evolved over the years and has contributed to improved treatment for bleeding disorders and a safer blood system for everyone. This Global Forum identified a number of priorities moving forward:

- Novel long-acting products entering the market will bring forth new treatment paradigms and opportunities to individualize therapy. Patients and treaters will require education on the different products and their benefits or trade-offs, so that they can make informed decisions.
- Health authorities will need to be educated on the novel therapies and the benefits in terms of improved efficacy, reduced frequency of treatment, reduced treatment burden, improved long-term outcomes, and cost-effectiveness compared to existing treatment.
- The bleeding disorders community must work together to collect data on what level of treatment is appropriate. This is a critical opportunity to reassess the optimum treatment and trough levels needed to achieve the absence of bleeds so that people with bleeding disorders can live normal lives.
- Clinical freedom and product choice based on the patient's treatment, condition, and preferences are essential and must be protected. Patients can have venous access problems or adverse reactions to certain products, and require access on an individual named patient or special access basis.
- Effective viral inactivation and detection processes are critical to safeguard recipients of blood products from new and emerging viruses. Ongoing surveillance of treatment products is essential to ensure continued product safety and detect emerging threats to the blood supply.
- There remain vast global disparities in availability of factor concentrates and access to treatment. The WFH's Project Recovery will produce safe factor concentrates for the developing world, and provides a model for developed countries, blood transfusion services, and industry partners to work together to provide life-saving medicines to the developing world.

DAY 1: SEPTEMBER 26, 2013

Welcome and Opening Remarks

John Bournas, Executive Director and CEO of the World Federation of Hemophilia (WFH), welcomed more than 120 participants to the 8th WFH Global Forum on the Safety and Supply of Treatment Products for Bleeding Disorders. This year's program highlighted current issues and developments related to the safety and sustainability of plasma products, clinical and economic aspects of novel treatment products, product choice, and the impact of regulatory factors on product access.

In addition to the latest on clinical research and state-of-the-art technologies, the Global Forum also focused on the ever-present issue of access to treatment in developing countries and the role of WFH in advancing blood product safety and supply globally. "About 75% of people in the world who have bleeding disorders are not diagnosed and are without access to proper care," Mr. Bournas noted. "Our ongoing Close the Gap campaign aims to highlight this need and to close the gap." He called upon participants to consider joining the campaign and announced that WFH patron Jan Willem André de la Porte would match and double all gifts made during the Global Forum. "It is our hope that his leadership and generosity will inspire you to join us," he said.

He thanked the sponsors of the 8th WFH Global Forum for having made this gathering possible: Baxter, the Foundation for America's Blood Centers, Héma-Québec, Ministère de la Santé et des Services sociaux du Québec (Québec Ministry of Health and Social Services), Novo Nordisk, Pfizer, and Swedish Orphan Biovitrum (SOBI).

SESSION 1: THE SAFETY AND SUSTAINABILITY OF PLASMA PRODUCTS

CHAIR: MAGDY EL EKIABY, MD, VICE PRESIDENT COMMUNICATIONS AND PUBLIC POLICY, WORLD FEDERATION OF HEMOPHILIA

The opening session focused on blood safety, global availability, and sustainability of plasma products, key issues which continue to drive scientific research and development of treatment products for bleeding disorders, and efforts by the World Federation of Hemophilia to improve access to safe and efficacious treatment worldwide. Several experts presented the latest research on viral transmission via plasma products, new technologies for viral testing, and viral inactivation of known and emerging pathogens. A debate on the future of plasma-derived products covered challenges and opportunities for the global plasma industry in view of rapid developments in biotechnology and the imminent arrival of new recombinant factor products on the market. In addition, the WFH's Project Recovery, a new humanitarian aid initiative to transform unused cryoprecipitate from the developed world into safe factor concentrates for the developing world, was officially launched.

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

This is the 8th WFH Global Forum. Including this Forum, how many have you attended?

All eight	10%
Five to seven	4%
Two to four	32%
This is my first Forum	53%

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

Inhibitors	35%
Supply/access to treatment products	56%
Pathogen transmission	4%
Other	6%

What do you think is the biggest safety threat today?

Inhibitors	58%
vCJD	0%
Viral transmission	9%
Unknown pathogens	32%

What do you think is the biggest supply threat today?

Price	73%
Regulatory issues	18%
Lack of manufacturing capacity	1%
Other	7%

Do you believe parvovirus B19 and hepatitis E are of concern regarding the safety of fractionated plasma products?

Yes	39%
Maybe	33%
No	21%
Don't know	7%

Safety and Supply – A WFH Focus

DAVID PAGE, WFH TREATMENT PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE

David Page provided a retrospective of the WFH Global Forum over the last 13 years, from its inception in 2000 to the present, in terms of looking at blood safety and supply issues. The first Global Forum took place in Montreal in April 2000, attended by hemophilia organization leaders from around the world, leading scientists, health and regulatory agency officials, and industry representatives. At that forum, different perspectives from the developed and developing world showed the issues and tensions surrounding blood product safety and increased access. Mark Skinner, then president of the U.S. National Hemophilia Foundation, took a strong stance of zero tolerance regarding risk of contamination in blood products; whereas Ashok Verma, founder of Hemophilia Federation India, decried the lack of access to blood products in the developing world. This exchange set the framework for the work of the WFH Blood Product Safety, Supply and Availability Committee and subsequent global forums.

The second WFH Global Forum was held in Montreal in January 2002 in the context of a major global shortage of FVIII concentrates due to a plant shutdown. It was also a critical time of grave concern about variant Creuztfeldt-Jakob disease (vCJD) in the blood system. While there had been no cases yet, research on some animal models showed that vCJD transmission was possible—and this was in fact borne out over the next few years.

The third WFH Global Forum was held in Budapest in September 2003, in conjunction with a regulatory workshop to train regulators in Eastern Europe. At that time, there was great debate within the global bleeding disorders community about plasma collection from remunerated plasma donors compared to voluntary, non-remunerated blood collection, and discussion about whether national self-sufficiency in plasma products was a desirable and practical goal. At the fourth WFH Global Forum in Montreal in 2005, the community began to look at utilization issues, particularly how the vast consumption of factor concentrates in the developed world affected the availability of products in the developing world, where there was little access to safe and effective treatment.

The fifth WFH Global Forum in 2007 focused on the issue of inhibitors. The main safety issue was no longer the transmission of viruses through blood products, but rather the risk of development of inhibitors to blood products. In addition, this forum examined biosimilars and concerns related to regulatory assessment of these follow-on biologics, and presented research on long-acting factor products which gave reason for great optimism for a new generation of treatment products.

In the wake of the 2007-2008 global financial crisis, the sixth WFH Global Forum in September 2009 focused on health technology assessments and hemophilia treatment outcome assessments, and clinical evidence supporting the case for the use of factor concentrates and prophylaxis, especially in adults. The seventh WFH Global Forum in 2011 looked at broader issues in blood collection including donor deferral of men who have sex with men, a current debate in many parts of the world. There was a lot of excitement about progress made with the next generation of longer-acting factor products, which would be further explored at this eighth WFH Global Forum, among other current topics and issues in bleeding disorders treatment safety, supply and access.

New Technologies For Virus Testing: Where Donor Screening Is Going

THOMAS R. KREIL, PHD, SENIOR DIRECTOR OF GLOBAL PATHOGEN SAFETY, BAXTER BIOSCIENCE

Over the last 30 years since the discovery of the human immunodeficiency virus (HIV) and the routes of transmission, the risk of contracting the HIV, hepatitis B (HBV) and hepatitis C (HCV) viruses through blood transfusions and plasma-derived products has declined exponentially due to the implementation of viral screening and testing and technological advances over time. Measures such as revised donor deferral criteria, HIV and HCV antibody screening, surrogate testing for HCV, HIV antigen testing, and HIV and HCV nucleic acid testing have greatly increased safety margins and reduced the possibility of contracting these viruses through blood transfusion and blood products by 100 to 10,000 times, depending on the virus. However, there are still many limitations. The sensitivity of these tests is such that a non-reactive/negative test result does not necessarily mean that there is no virus. The tests are also limited to known viruses. Current methodologies only test and provide results for the specific pathogens being sought; this may change with some of the new technologies.

Virus Detection

Nucleic acid testing (NAT) is among the current state-of-the-art technologies available. It is more sensitive than conventional tests and shortens the window period for viral detection. The NAT test can detect the presence of low levels of viral genetic material (minimal viral loads) in blood before antibodies are detectable. It allows for screening and detection of HIV, HAV, HBV, and HCV earlier in the infectious cycle and decreases the possibility of viral transmission via blood transfusion. Viral load testing based on the polymerase chain reaction (PCR) method is extremely sensitive and reduces the window period for detecting HCV from three months to approximately three weeks, and can identify HIV in the blood within two to three weeks of infection.

The emergence and spread of West Nile Virus (WNV) in the United States from the first reported cases in 1999 and onward serves as a reminder of the limitations of current tests and technologies. WNV was first identified in the West Nile sub-region of Uganda in 1937. It was considered a minor risk to humans until the mid-1990s, when it began to spread to the Western hemisphere and globally. In 2002, the U.S. identified over 3,500 cases of clinical WNV infections and 240 cases of WNV-related deaths that year. WNV is primarily mosquito-borne but was subsequently detected in blood donations and transmission by blood transfusion was identified among additional transmission methods. Since then, many blood banks have initiated routine WNV screening of blood and plasma donors and manufacturers have introduced NAT screening tests for WNV.

Blood Safety Tripod

Viral safety of blood products depends on a "blood safety tripod" of donor selection, testing of blood donations, and virus reduction. Donor screening and selection help reduce risk to a limited extent. With WNV, donor selection allows a 20% risk reduction because about 80% of viremic donors are asymptomatic. PCR testing of individual blood donations provides 100% risk reduction, while mini-pool PCR testing provides a 93% risk reduction.

Virus reduction and inactivation during the manufacturing process safeguard blood products from viral contamination. Virus reduction is fairly generic, while inactivation measures can remove both known and undetected pathogens. WNV and similar viruses (e.g., dengue fever virus, yellow fever virus, tick-borne encephalitis) require their own specific tests but the reduction capacity for these viruses is very similar. Solvent detergent, vapour heating, low pH incubation, and pasteurization methods have all effectively inactivated WNV. Plasma-derived products therefore can enjoy significant

safety margins even without specifically testing plasma for viruses such as WNV. While it can be argued that virus reduction is most important to ensuring the safety of plasma products, it is important to note that this is not the case for transfused blood products, where testing is critical.

New Technologies for Virus Detection

Several new viral detection technologies are being advanced: multiplex PCR, protein and nucleic acid arrays, and deep sequencing/massive parallel sequencing. These applications have both potential and shortcomings.

Multiplex PCR

Multiplex PCR is a testing platform that accommodates multiple analytes for different targets in a single amplification reaction and uses different fluorescent dyes in parallel to amplify multiple target sequences at the same time. It offers rapid exponential amplification and exceptionally high sensitivity and is currently used in plasma testing for certain viruses (HIV, HAV, HBV, HCV, B19V). Multiplex PCR is appropriate for testing a limited number of targets of less than 30 agents. It has potential for applications beyond current use.

Protein and Nucleic Acid Arrays

Protein and nucleic acid arrays enable testing with multiple analytes on a single chip; over 100,000 analytes can be probed on a chip 1 cm^2 in size. However, while these arrays can process more targets, they offer less sensitivity. Another limitation is that the targets and parameters for detection must be decided in advance. This methodology can be useful in specific circumstances where there is an understanding of the viruses possibly involved, and the primary aim is confirmation and diagnosis. However, the technology is fairly expensive so it may find only a very small niche of applications.

Massive Parallel Sequencing

Next generation sequencing, also called deep or massive parallel sequencing, represents the next generation of virus testing. It is the most advanced method of genome sequencing and enables full sequencing and identification of viruses and other adventitious agents, including new and unknown agents. These extremely high throughput instruments produce a vast amount of genomic data and have the ability to fully sequence thousands of genes in a single test. Massive parallel sequencing can generate thousands to billions of reads in a matter of days or weeks, making it a powerful tool for detecting pathogens in the clinical setting. However, the benefits of the faster technology are offset by the substantial time required to analyse all the data generated, which can take many weeks or months. Interpretation of data will be one of the biggest challenges. However, this technology has great potential and will find commercial applications for routine purposes.

In the last two years, massive parallel sequencing has led to the identification of about six new viruses. One important discovery was the identification of an adventitious virus, the porcine circovirus (PCV), in a live attenuated rotavirus vaccine available on the market. Once PCV was detected, the regulatory recall was swift and there were no negative consequences; the vaccine is still available on the market. These technologies will have future applications and benefits for the analysis of less-known cell substrates.

Many efforts are being made by scientists to advance the potential of the new technologies. Within the U.S. Food and Drug Administration, the Center for Biologics Evaluation and Research and the Office of Blood Research and Review have an ongoing research priority project focused on the evaluation of emerging technologies for high sensitivity detection and novel reduction methods for infectious agents in blood and blood products. There are important distinctions between blood products and plasma-derived products. For blood transfusion products, testing is the vital contribution and efforts to detect virus contaminants in blood for transfusion are a lot more rigorous than for the

screening of plasma. For plasma, virus reduction and inactivation during the manufacturing process are critical to safety margins. Still, despite robust viral inactivation steps during manufacturing, with new and emerging agents, it is important to verify assumptions and investigate whether the reduction methods will hold up.

The new virus testing technologies carry much potential, but their specific applications and usefulness (i.e., routine testing, outbreak investigation, virus discovery) still need to be determined and evaluated. It will be a challenge to determine whether viral signals are related to cell line infectivity and/or pathogenicity, and whether it is relevant for safety. Other challenges are reliability, validation, and licensing of the new technologies, and distinguishing the true and relevant signals from false signals.

Discussion

Dr. Flora Peyvandi of Italy's Angelo Bianchi Bonomi Hemophilia and Thrombosis Center expressed some concerns about the use of next generation sequencing for virus detection and discovery. In the last 10 years, there have been many studies done but the meaning and significance of vast amounts of the data collected has not been understood until recently. With known pathogens, target sequencing can be performed and next generation sequencing is really not needed. For new, previously unknown pathogens, it is extremely risky to perform next generation sequences without really knowing the use of the data. The interpretation of the new viral sequences is a big challenge. Controls are also a big issue because control regions can be different.

Dr. Kreil concurred. Multiplex PCR has served the bleeding disorders community very well and its uses and application could be broadened. Next generation sequencing is a powerful technology for discovering new viruses but the data is not well understood; there is currently much speculation and many hypotheses being generated on new unknown viruses but their associations may never be proven. The application of next generation sequencing may not necessarily be of great service to the bleeding disorders community. However, it is a highly competitive research area that is well supported by research funding mechanisms.

Transmission of B19 and Hepatitis E by Plasma Products

MICHAEL SOUCIE, PHD, DIVISION OF BLOOD DISORDERS, CENTERS FOR DISEASE CONTROL AND PREVENTION, USA

Epidemiologist Michael Soucie gave an overview of parvovirus B19 (B19V) and hepatitis E (HEV), the characteristics that make these particular viruses an issue in plasma-derived products, evidence on transmissibility, and current prevention strategies.

Parvovirus B19

B19V is a ubiquitous virus that typically causes a benign flu-like illness and occurs most frequently in childhood without long-term effects. It is highly prevalent in the general population; over 90% of people are exposed to B19V and experience an infection by age 20. The symptoms of infection are macular papillary eruption and a "slapped cheek" appearance. Clinical features include fever, chills, headache, myalgia, rash, and arthralgia. Adults exposed to B19V, especially women, can develop acute and chronic arthritis. Pregnant women who get B19V infection have a risk of miscarriage. Certain groups have a high risk of developing fulminant hepatitis and aplastic anemia from exposure. Infected individuals have high levels of viremia. There is evidence that some people get B19V infection but show no symptoms. Asymptomatic individuals with high viremia who donate blood contaminate the plasma pool.

B19V is a non-enveloped, single-strand DNA virus; it is relatively resistant to current viral inactivation methods due to its extremely small size (19-23 nm); most currently available products are not routinely filtered but, if done, a 35 nm filter is most often used. A 2012 review of the literature on parvovirus transmission by blood concluded that the data provides evidence that B19V is able to survive current fractionation and inactivation processes. B19V transmission has been reported from red blood cells, platelets, fibrin sealant, and intravenous immunoglobulin (IVIG). A 2002 study by the U.S. Centers for Disease Control and Prevention (CDC), using data from its hemophilia surveillance system, found that children who had been exposed to plasma-derived products, as opposed to recombinant products or no products, were nearly eight times more likely to have immunoglobulin (IgG) antibodies to B19V.

Manufacturers began voluntary minipool plasma NAT screening in 2000. A 2007 study by the U.S. Food and Drug Administration, which tested factor products made by various manufacturers before and after the year 2000, found that overall the screening had lowered levels of B19V in most products. However, some products had relatively high levels of B19V, suggesting that perhaps they had not been PCR tested. Until recently, no study has evaluated the effectiveness of NAT screening in preventing B19V transmission to patients.

Dr. Soucie presented results from his seroprevalence study published in *Transfusion* this year, which showed evidence of the continued transmission of B19V in patients with bleeding disorders treated with plasma-derived factor concentrates since the implementation of NAT screening. The study looked at 1,043 young children with bleeding disorders (65% hemophilia, 31% von Willebrand disease, 4% other bleeding disorders). About 55% of the children had had one or more active bleeds in the last six months and therefore had likely been exposed to treatment products. About 33% of the children had never received any blood or blood products and served as the control subjects. B19V prevalence was higher among patients exposed to blood or blood products than patients exposed to recombinant products or no product, and even higher among patients exposed to both recombinant and plasma-derived products. About 50% of patients aged 7 had IgG antibodies. A multivariate analysis was performed and adjusted for differences in age, sex, race, treatment type, treatment frequency, year of testing, and hemophilia inhibitor status using logistic regression.

The analysis found that patients exposed only to plasma-derived products had a 70% increased risk of a positive test for IgG antibodies to B19V. The findings show that while the risk of B19V transmission appears to be lower with NAT screening, it may not be zero, and NAT screening cannot be expected to be effective against the transmission of unknown or emerging viruses with similar characteristics, such as HEV.

Hepatitis E

Annually worldwide, there are an estimated 20 million HEV infections, 70,000 HEV-related deaths, and 3,000 HEV-related stillbirths. HEV is found worldwide but its prevalence is highest in East and South Asia. HEV is very similar to hepatitis A (HAV) in terms of illness symptoms and transmission methods. In most cases, HEV is self-limiting but high-risk groups may develop fulminant hepatitis. Case fatality rate is several times higher for pregnant women, and babies have an increased risk of prematurity, low birth weight, and perinatal mortality. HEV genotypes 1 and 2 are highly endemic in developing countries, while genotype 3 has worldwide distribution, and genotype 4 is found primarily in Mexico and Asia.

A study among 604 residents of England and Wales showed an increase in HEV cases between 2003 and 2005. The epidemiology shows that most of the cases were associated with people who had travelled to endemic areas and returned with HEV infection. Since then, most HEV cases in the developed countries have been unrelated to travel and considered to be related to an endemic source.

A U.S. study using data from the 1988-1994 National Health and Nutrition Examination Survey looked at HEV prevalence by age and country of birth. It found rising prevalence with age. About 50% of people in the U.S. have been exposed to HEV.

HEV is transmitted primarily by the fecal-oral route, principally through ingestion of contaminated water. Other transmission routes include food-borne transmission from ingestion of products derived from infected animals, particularly swine. Three studies have documented transfusion of infected blood products and there have been cases of vertical transmission from woman to fetus.

HEV has been present in the population for over 20 years and there is evidence of transmission by blood. No screening test is available. HEV is a non-enveloped single-stranded RNA virus; like B19V, it is very small (27-34 nm). It is similar to HAV, which was previously been found to be transmitted by plasma-derived concentrates. Symptoms do not occur until one to two weeks after the virus enters the bloodstream; therefore, an asymptomatic person could donate blood and contaminate the pool.

Data from the CDC surveillance system for the safety of bleeding disorder treatment products show there have been no hepatitis or HIV infections linked to blood products since 1998. Blood specimens stored in a serum bank have been used in investigations to determine whether B19V is linked with porcine FVIII, a discontinued plasma-derived product previously used to treat patients with inhibitors; and to investigate the epidemiology and prevalence of West Nile Virus before it became endemic in the U.S. Ongoing surveillance of the population is extremely important to ensure continued product safety and detect emerging threats to the blood supply. Effective viral inactivation and detection processes will ultimately be the best weapon to protect users of blood products from infection with B19V and other new or emerging viruses.

Discussion

Regarding Dr. Soucie's study on B19V transmission in patients treated with plasma-derived products after the introduction of NAT screening, Dr. Johannes Blümel of the Paul-Erhlich-Institut in Germany asked whether the investigators could be certain that all of the children were treated with plasma-derived products that had been screened for B19V. In a similar study in Germany, researchers were not able to determine a clear-cut time and date when screening was fully implemented for all the products. European regulatory requirements for B19V NAT testing were introduced in 2004; however non-screened products were still available on the market for a period of years after the introduction of screened products. The rigour of NAT testing implementation also differed among manufacturers.

There is no certainty that all the patients exposed to plasma-derived products received screened products, Dr. Soucie said. The aim of the study was to evaluate the use of NAT screening for B19V and its effectiveness in protecting the patient population. It is possible that a patient could have received an unscreened product because of lack of full implementation of screening; for example, if a manufacturer did not implement NAT testing according to the regulatory standards and time requirements or a product was missed. The key points from the study are that B19V still got through into plasma-derived products after NAT testing began; therefore, the strategy was not 100% effective, which is the goal of screening strategies.

Dr. Blümel noted that a study on children with hemophilia treated with plasma-derived products in the 1990s, before plasma screening was implemented, found that by age 2, almost all had IgG antibodies to B19V. In comparison to the historical data, Dr. Soucie's data shows the progress in B19V screening and virus reduction. Dr. Soucie said safety has been greatly improved. Previously, hemophilia patients treated with plasma-derived products were 7.6 times more likely to have IgG antibodies to B19V;

NAT mini-pool screening has reduced this likelihood to 1.7 times. However, the ultimate goal is be 100% effective, and this may possibly require viral inactivation.

Thomas Sannié of l'Association française des hémophiles said France's National Authority for Health and Ministry of Health consider HEV as a serious issue and are mid-process in evaluating the exact risk. He noted that in addition to the HEV infection risks for pregnant women, there are risks for immunocompromised patients. In terms of HEV prevalence in the general population, one study on HEV in plasma donations from Europe and the U.S. suggested that 1 in 4,000 to 1 in 8,000 donors have HEV, while another estimate suggested 1 in 1,200 blood donors have HEV.

HEV exposure does not cause illness in most immunocompetent people but there are high-risk groups including immunocompromised patients, Dr. Soucie agreed. The bleeding disorders population is a high-risk group because a percentage of patients have underlying liver disease from HCV infection through blood products. Regarding prevalence, one of the challenges is that HEV testing is somewhat problematic; many studies have been done around the world and showed great variation in prevalence, which may be related to the testing and assay methods.

Dr. Thomas Kreil said HEV testing is complicated because researchers have so far been primarily looking for antibodies but it is now understood that anti-HEV antibodies vary by two- to threefold with respect to positivity. Assays also differ in sensitivity and specificity. The Wantai assay is very reliable; recent epidemiological studies with this assay produced positivity rates of 10% in England and 50% in the south of France. A recent study in the Netherlands found the presence of viremia in 1 in 2,500 to 1 in 5,000 blood donors and there is a large study ongoing in the U.S. which may provide a much clearer picture of HEV viremia occurrence in blood donors.

Mr. Sannié said given that HEV is prevalent in 1 in 4,000 to 8,000 blood donors, should there not be more events of transfusion-transmitted HEV? A recent pharmacovigilance report only identified HAV, HBV and HCV as post-transfusion concerns; whereas HEV was classified as a non-viral hepatitis. A key message to physicians is that it is important to look carefully for HEV, in case this virus is being under-reported. The HEV genotypes 3 and 4 circulating in the developed countries are zoonotic and seem less virulent than genotypes 1 and 2, which are exclusive to humans and have caused severe HEV outbreaks in Sudan, Pakistan, and India. However, HEV has not been vigorously surveyed. One current theory is that there could be a difference in virulence between the genotypes.

Dr. Michael Makris of the University of Sheffield in the U.K. recounted that an elderly patient with severe hemophilia on prophylaxis had developed acute HEV infection but no other cases were found. The conclusion was that there are likely sporadic cases that have nothing to do with the individuals having a bleeding disorder. Dr. Soucie underlined the importance of ongoing surveillance in order to minimize transmissible risks for patients with bleeding disorders.

Inactivation of Non-Enveloped Viruses such as Parvovirus B19 and Hepatitis E Virus

JOHANNES BLÜMEL, PHD, HEAD OF VIRUS SAFETY SECTION, PAUL EHRLICH- INSTITUTE, GERMANY

Dr. Johannes Blümel gave an overview of viral inactivation of non-enveloped viruses, focusing on the hepatitis A virus (HAV), hepatitis E virus (HEV), parvovirus B19 (B19V) and parvovirus 4 (PARV 4).

Hepatitis A Virus

Hepatitis A is an acute liver infection that can cause mild to severe illness. It is the most common form of acute viral hepatitis and highly prevalent in some parts of the world. Some people do not display noticeable symptoms; therefore, HAV can enter the plasma pool via asymptomatic viremic donors. Most children have few or no symptoms. The epidemiology of HAV is changing. Public health measures on water quality and supply, hygiene, and sanitation, as well as the availability of HAV vaccination have resulted in lower seroprevalence in Europe and North America.

Viremia (the presence of virus in the blood) is important when trying to estimate plasma safety. HAV viremia is very low, generally around 10^5 GE/mL. Cases of HAV transmission have been reported, including in Germany in 1997 via a solvent-detergent treated FVIII product manufactured without a robust inactivation step. There is debate as to whether blood donations should be subject to rigorous NAT screening for HAV. There are currently no uniform regulatory requirements. HAV screening must be ultra-sensitive for large plasma pools. NAT screening helps cut off very high viremic donations and helps ensure the manufacturing process is not overloaded with viruses. Most products on the market commonly require at least one robust HAV inactivation step. HAV could potentially be a model for estimating inactivation of other viruses including unknown viruses.

Hepatitis E Virus

HEV is highly prevalent in endemic regions. HEV genotype 1 is found primarily in Africa and Asia; genotype 2 in Africa and Central America; genotype 3 in many parts of the world; and genotype 4 mainly in parts of Asia. Genotypes 3 and 4 generally present low clinical risk for immunocompetent individuals, with some exceptions. HEV viremia is low, up to 10^7 GE/mL. A pool of 1,000 plasma donations usually has a viral load in the range of 10^2 GE/mL to 10^5 GE/mL. Transmission cases via non-inactivated blood components (red blood cells and platelets) have been documented.

There is currently no NAT screening for HEV; therefore, it falls to blood transfusion services to decide whether screening is warranted; for example, in areas with a high incidence of new infections or for blood products for high-risk recipients. The clinical risk needs to be defined. Until recently, no vaccine was available; China has developed a vaccine which became available at the end of 2012 and appears to be effective. There are other international efforts including a vaccine that has been primarily developed against the virulent genotypes 1 and 2, which circulate in India and Pakistan. At present, it is believed that there could be some cross-protection of the virulent genotypes.

Parvovirus B19

B19V is contagious before infected individuals develop symptoms. B19V viremia can be very high, up to 10^{12} GE/mL. It is extremely difficult to inactivate such a high viral load. Transmission cases through dry-heat treated plasma products have been documented and tracked to large plasma pools overloaded with B19V; heat treatment procedures were not sufficient to inactivate B19V completely.

A high-titre B19V NAT test (pool limit of 10^4 GE/mL) is recommended by regulatory agencies for source and recovered plasma to be used in the further manufacturing of plasma-derived products, but it is a voluntary safety measure and not required of industry. Screening of recovered plasma for plasma fractionation is done in some countries using minipool testing. Clinical risk is not well defined but is low for immunocompetent individuals.

Parvovirus 4

PARV 4 was discovered in 2005 in a blood sample obtained from an HIV/HCV co-infected individual enrolled in the University of California San Francisco's Options Project, a research study on people at risk for HIV infection through injection drug use or high-risk sexual contact. Most PARV 4 infections are asymptomatic. PARV 4 has a moderate/high prevalence and incidence rate. A recent study of U.K. blood donors found about 2-3% of blood donors to be IgG positive. Viremic donors sometimes suffered from as many as five infections; thus far the specific disease associated with PARV 4 remains unknown. There could be some association between PARV 4 and HIV, HCV, and HBV risk groups but this has not been confirmed.

Clinical risk is unclear. PARV 4 viremia is somewhat high, similar to HEV but not as high as B19V, with a range of 10^5 GE/mL to 10^8 GE/mL found in blood donations and 10^5 GE/mL in plasma pools of 2,000 to 10,000 donations. A 2009 study found frequent PARV 4 transmission by virally inactivated factor concentrates and identified PARV 4 as a transfusion-transmissible agent that is resistant to viral inactivation; there are also other ongoing studies. No NAT screening is performed for PARV 4. There is speculation on whether virus reduction methods that are effective for other parvoviruses would work with PARV 4. There is currently no PARV 4 vaccine.

Methods for Viral Inactivation/Removal

The main virus reduction methods are liquid heat treatment (pasteurization), dry heat treatment, virus filtration, and pathogen inactivation.

Liquid Heat Treatment (Pasteurization)

Pasteurization (10h 60° in albumin) appears to work well for HAV. In a 2012 study, German researchers investigated different model viruses, strains, and inactivation methods, and found pasteurization works better with some strains than others. A similar Japanese study in 2013 also demonstrated differences depending on the model viruses and strains. The studies, along with unpublished data from the Paul Ehrlich Institute, demonstrated 4 to 6 log reduction of HAV during FVIII production. There has been little investigation of pasteurization of HEV. Data from Japan this year showed about 1.5 log reduction; pasteurization appears more effective with HAV than HEV. The plasma industry should collect and produce data on the effectiveness of viral inactivation steps with HEV, in order to be able to make risk estimations and determine the best way to inactivate HEV. Pasteurization worked well to inactivate B19V and porcine parvovirus (PPV), but appears less effective for PARV 4.

Dry Heat Treatment

Dry heat treatment leads to stabilization of viruses. Critical parameters are temperature and residual moisture. If residual moisture is too high, it causes damage/loss of product potency; if residual moisture is too low, the product is very stable but there is no virus inactivation. At the proper temperature (80°C for 72 hours or 100°C for 30 minutes) and moisture controls (0.1 to 2%), dry heat treatment can achieve good inactivation of a broad range of lipid enveloped viruses (HIV, HBV, HCV) and some non-enveloped viruses (HAV, PPV, B19V). With HAV, there is substantial loss of infectivity at the initial freeze-drying process followed by viral inactivation at the heating phase.

Less is known about the effectiveness of dry heat treatment in HEV inactivation. A 2008 study found HEV sensitivity varied greatly depending on heating conditions, with HEV inactivation to below the detection limit within 24 hours at 80°C in fibrinogen concentrate. However, studies related to FVIII and FIX concentrates have not been done. Industry should be called upon to produce such data. Dry heat treatment does not completely inactivate parvoviruses; it achieves good inactivation of animal parvoviruses such as PPV and of B19V in a tightly controlled environment.

Virus Filtration

Small pore nanofiltration is very promising technology. A current limitation is that filtration procedures are ineffective with complex coagulation factors such as von Willebrand factor, which does not pass through the nanofilter and/or loses potency. However, other highly purified FVIII products can pass through the nanofilter, and parvovirus filters have been introduced for a few high purity FVIII products. Nanofiltration achieves efficient removal of HAV and HEV. It also efficiently removes PPV, which is accepted as a model for B19V. A recent study comparing 20 nm nanofiltration of PPV with B19V, very similar viruses of the same size, showed that around 4 log reduction can be achieved. However, some of the smaller viruses can still penetrate the filters because their size is similar to the filter pore size. With tight controls, it is possible to get an effective and clear signal reduction of virus.

Pathogen Inactivation

Pathogen inactivation has been introduced for platelets, blood cells, and plasma; it is not intended for coagulation factor production. The processes use psoralen derivatives and ultraviolet light, riboflavin and ultraviolet light or methylene blue to inactivate pathogens in blood and blood components and seem to be very effective against all the known enveloped viruses; HCV, HIV, and WNV are very efficiently inactivated. A key challenge is that the nucleic acid modifying substance must penetrate the virus shell in order to contact the viral DNA/RNA. B19V inactivation seems possible but may not be complete. There is no inactivation of non-enveloped viruses such as HAV, animal parvoviruses, and enteroviruses.

In summary, these viral reduction methodologies range in effectiveness for different viruses. There is considerable evidence of good HAV inactivation through liquid pasteurization, dry heat treatment, and small virus filtration. There is currently a lack of risk assessment of plasma products for HEV and HAV. HEV, HAV, and B19V can be removed by nanofiltration and speculation is that PARV 4 would likely be similarly removed. It appears that B19V can be inactivated by liquid heat treatment and dry heat treatment.

Project Recovery

DAVID PAGE, EXECUTIVE DIRECTOR OF THE CANADIAN HEMOPHILIA SOCIETY (CHS)

The World Federation of Hemophilia launched Project Recovery, a new humanitarian aid project in partnership with Canadian Blood Services (CBS) and plasma manufacturers Biotest AG and Grifols, which will turn unused blood products from Canadian blood donations into hemophilia medicine for patients in developing countries with little or no access to these life- and limb-saving medicines. Project Recovery, first conceived by the Canadian Hemophilia Society (CHS), has become a reality after many years of effort and determination. David Page gave an overview of the project's goals, challenges along the way, and the benefits they will bring to patients in developing countries.

The idea of Project Recovery arose following the introduction in Canada of recombinant FVIII. By 2000, Canada was nearly 99.9% reliant on recombinant FVIII for hemophilia A treatment and obtained von Willebrand factor from commercial suppliers. Canadian Blood Services was sending its recovered plasma for fractionation by Bayer in the United States, and the cryo-paste resulting from fractionation of the recovered plasma was discarded. The Canadian Hemophilia Society approached the WFH about turning the discarded cryoprecipitate into medicine for humanitarian use in the developing world, and the topic was discussed at the first WFH Global Forum in 2000.

However, when Canadian Blood Services asked Bayer about the feasibility of using the discarded cryo-paste to manufacture FVIII concentrates, the company reported that the yield would be much lower than the yields from source plasma and recovered plasma. An additional complication was that Canadian import and export regulations in regards to plasma stipulated that the finished product could only be used in Canada; it could not be exported to other countries.

All the same, CBS expressed interest in the project. At the time, the blood collection agency also had plans to increase plasma collection through plasmapheresis and considered this project to be a worthwhile opportunity and contribution to the developing world. It was also a time when variant Creutzfeldt-Jakob disease (vCJD) outbreaks in Europe was causing great fear of vCJD transmission through blood products. The unused Canadian plasma was the single largest untapped resource for safe FVIII and FIX concentrates in the world. However, there were several ethical issues, which WFH and CHS representatives outlined at a meeting with CBS. Could Canada export its plasma-derived FVIII concentrates? Given that Canada was in effect wholly reliant on recombinant factor, would doing so be ethical? Would Canadian blood donors be in agreement with these leftover proteins being used outside Canada? Meanwhile, Ashok Verma, of Hemophilia Federation India, wrote to CBS on the matter: "We are going without plasma. Please make this project a reality."

In 2003, at a CBS plasma protein product strategy meeting, CHS presented a proposal which was included in the meeting notes submitted to the CBS board of directors. There was interest at CBS but no concrete plans to increase plasma collection nor plans to adapt collection practices to increase FVIII yield; challenges included Canada's vast territory and outlying collection sites and sometimes slow times to freezing in the blood collection process.

The WFH subsequently branded the project as Project Recovery and published a white paper, and eventually found a partner in South Africa's National Bioproducts Institute, which had a big need for safe cryo-paste. The plan was for Talecris, which had acquired Bayer and now fractionated plasma from CBS, to ship the unused Canadian cryo-paste to South Africa to manufacture FVIII concentrate for the South African market. The project at that point became endorsed by the Global Collaboration on Blood Safety of the World Health Organization.

However, there were numerous technical hurdles which were difficult to overcome and collaboration stalled. Meanwhile, the CBS switched to buffy-coat component production to produce platelets from whole blood collections, which allows platelets to be processed within 24 hours (as opposed to 8 hours with the platelet-rich plasma method), which results in a higher yield of platelets but a 50% reduction in FVIII yield. All of the testing that had been done with the plasma to date was no longer valid. After eight years, the project had made no progress.

The WFH again began to look for new partners and with the cooperation of CBS more batches of cryo-paste were sent to European fractionators to gauge the quality and yield, but none of these efforts panned out. A breakthrough came in 2010 when Biotest AG, based in Germany, became interested in getting involved. In March 2010, Biotest processed a batch of Canadian cryoprecipitate and concluded that there was adequate yield; and that with certain improvements, harvesting could be improved. A large batch was retested and shown to be viable. Biotest was also very helpful in working through the international regulatory issues: recovered plasma originating from Canada would be sent to the United States for fractionation, then surplus cryoprecipitate would be sent to Germany to produce factor products. Biotest worked with the German regulatory agency, the Paul Ehrlich Institute, to address difficult issues such as transportation of the intermediate products and product marketing by Biotest, and distribution to the developing world.

Meanwhile, CBS worked to ensure that its insurers were comfortable with the liabilities and also conducted surveys and focus groups of blood donors, who showed clear support for the initiative. Legal contracts were drawn between the different stakeholders. Another hurdle came with the sale of the U.S.-based Talecris to Grifols, based in Germany. The viral testing practices between CBS, Grifols, and Biotest needed to be aligned to meet Biotest's requirements. Perhaps the biggest obstacle was that the fractionation contracts between CBS and its two custom fractionators, Grifols and CSL Behring, were coming to an end. There was no guarantee that Grifols would have Canadian plasma to initiate the project. In the end, the contracts were negotiated and Grifols has maintained a share of the plasma and is moving forward as a partner.

At present, the exact yield is not known but appears very promising. Grifols is harvesting cryo-paste from 150,000 litres of plasma annually. Biotest will receive the first shipment of its cryo-paste in the coming months. Biotest will retain a portion of the FVIII product to cover their total fractionation costs, and CBS and the WFH will receive the balance. It is expected that CBS will receive the first donations of the FVIII product, called Haemoctin®, in early 2014. The product will also be distributed directly from Biotest to WFH recipient countries. It is estimated that in the first year, this will provide 5 million IUs of FVIII concentrate to the WFH Humanitarian Aid Program and in subsequent years, with possible increases in plasma collection levels, quantities could increase.

Project Recovery is a cost-neutral project. The contractual agreement means that 150,000 litres of Canadian cryoprecipitate will go to Project Recovery via Grifols and Biotest. At the same time, CBS is allocating another portion of Canadian plasma to CSL Behring, which is producing von Willebrand factor for the Canadian market. Likewise, Héma-Québec is using its share of plasma to make FVIII and von Willebrand factor for the Quebec market, which means that 100% of Canadian cryoprecipitate is now being recovered and used.

Many individuals have contributed invaluable effort and expertise to this project over many years: WFH Past President Mark Skinner, who promoted the project throughout his term from 2004-2012, and WFH Senior Public Policy Officer Mark Brooker, who coordinated the technical negotiations with CBS and industry partners; Bill Mindell, CHS representative with the CBS Board of Directors; Svenja Barckhausen, Peter Pustoslemsek and Joachim Herborg of Biotest; David Sorell of Grifols; and Chantal Couture, Keith Buchanan and Rick Trifunov of Canadian Blood Services.

Ian Mumford, Chief Operating Officer, Canadian Blood Services

Canadian Blood Services is a proud partner in Project Recovery, an initiative that shows the strength of the relationships among stakeholders in the blood industry not only in Canada but also around the world, said Ian Mumford. He credited the determined efforts of the CHS, led by David Page and Bill Mindell, for Project Recovery's important milestone at this point in time. "The journey was not easy and certainly was not quick," he said. "We've had to break our own path, find our way literally across borders, and navigate the complexities of international law and regulations—but we've made it and the end result has definitely been worth the effort."

Thousands of people with hemophilia around the world have little or no access to life-saving treatment because of lack of factor concentrates in developing countries. They suffer with crippling pain and many die from internal bleeding. "With the amount of plasma left over from the manufacturing of products for Canadian patients that was simply discarded, we were quite literally tossing away potential to help. That's no longer the case and soon this medicine will find its way to those who desperately need it," he said. "We are fortunate to live in Canada, and with that comes an obligation to help those who are less fortunate. Project Recovery allows us to maximize the generous gift that our donors roll up their sleeves to give us every day. We've set an example for other blood operators around the world, and we do hope that they will follow suit."

Svenja Barckhausen, Director, Plasma Procurement, Biotest

Biotest is one of the smaller global plasma product manufacturers and is very proud to be a part of Project Recovery, said Svenja Barckhausen. "When we were approached by CBS and the WFH, we saw our size and the flexibility that comes with smaller size as an opportunity to make this happen. There were a lot of obstacles and it was not easy to bring to reality, but we looked at the material and found a way to process it."

Biotest has put great effort into Project Recovery even though there is no revenue or profit. It allows the company to make a meaningful contribution to patients, doctors and the WFH, of a special value without profit motivation. Nevertheless, the hope is that the product will be acknowledged and that it will help pave the way to some markets where Biotest is currently not registered. "All the way through the chain of negotiation, planning, investigation, and development, quality came first and safety always was the first aim," she added.

Alain Weill, President, World Federation of Hemophilia

Project Recovery fits perfectly within the WFH's global mission of Treatment for All, which is advanced through the WFH Humanitarian Aid Program and other initiatives, said Alain Weill. The WFH Humanitarian Aid Program coordinates pharmaceutical industry donations of FVIII and FIX concentrates and distributes these life-saving medicines to countries where there is most urgent and obvious need. However, due to a variety of factors, these product donations are irregular, vary in volume, and usually have a very limited and much shorter shelf life. In Project Recovery, the WFH has achieved a momentous milestone. WFH will now have a product with full shelf life and predictable volumes every year, which will enable the organization to better plan humanitarian aid donations and achieve more benefits. "The availability of factor concentrates in these countries will enable doctors to treat hemophilia and encourage them to diagnose patients," he said. "It will also allow governments to see and realize the benefits of factor concentrates and encourage them to procure factor products for hemophilia."

Alok Srivastava, WFH Vice President Medical

The importance of comprehensive care for people with hemophilia, including treatment with clotting factor concentrates, is well known. Project Recovery will have significance in parts of the world that currently have scant or no access to factor concentrates. Globally, about 7 billion IUs of factor concentrate are currently being produced annually. There is a huge disparity in availability and demand. Most of the global factor supply—about 5.5 to 6 billion IUs—is consumed in developed countries with a total population of 1 to 1.5 billion people, leaving 1 to 1.5 billion IUs available to about 6 billion people in developing countries. The WFH has worked to develop and implement sustained and self-supported hemophilia comprehensive care in over 100 countries around the world. The key challenge is to introduce clotting factor concentrates to developing countries to help health authorities and treaters realize the significance of factor products in the treatment of bleeding disorders.

On behalf of the WFH, he thanked Canadian Blood Services, Canadian blood donors, and industry partners Biotest and Grifols for their essential contributions to Project Recovery; and on behalf of patients, physicians and healthcare workers in the developing countries, he thanked the WFH for pursuing this endeavour. He expressed hope that other countries, blood transfusion services, and industry partners will follow the course set by Project Recovery.

Discussion

Currently in Australia, about 100 million IUs are effectively being destroyed and while this type of development is recognized and keenly sought by Australian blood services and the national plasma fractionator, the main impediments are related to political governance challenges and resistance from the state and territorial governments, said Albert Farrugia. It appears that the impediments encountered in advancing Project Recovery were mostly related to regulations, and the governance structure of Canadian Blood Services is such that it did not face such impediments from provincial governments.

Ian Mumford explained that Canadian Blood Services was created 15 years ago as a not-for-profit blood services organization funded by provincial and territorial ministries of health but operating at arm's length from government, following the recommendations of the Krever Commission of Inquiry on the Blood System in Canada. Operational decisions are made by CBS according to the organization's guiding principles and with approval from the CBS board of directors; provincial and territorial governments are kept informed along the way and have been satisfied with this governance structure.

Dr. Steven Pipe of the University of Michigan C.S. Mott Children's Hospital, Ann Arbor, USA, asked if there is quantitative knowledge of the potential untapped blood resources outside of Canada, i.e., an estimate of the amount of unused plasma discarded from fractionation processes worldwide. Dr. Srivastava noted that an estimated 10 million IUs are discarded in Australia, and estimated that the untapped plasma potential worldwide could be in the range of 1 to 2 billion IUs. Prof. Farrugia estimated that about half of all plasma collected for fractionation worldwide is being used to extract and produce FVIII products. "This is a back-of-the-envelope figure but what is interesting is that this is exactly the same proportion that existed in the industry 30 years ago," he said.

Dr. Pierre-François Falcou of LFB Biomédicaments in France said the biopharmaceutical company had tried to be part of the project. One of the major hurdles for a transnational or transcontinental company is to secure regulatory approval in the country of the manufacturer. Germany's regulatory agency, the Paul Ehrlich Institute, must be acknowledged for its involvement, collaboration, and role in the project's success.

Brian O'Mahony, Chair of the WFH Treatment Product Safety, Supply and Access Committee, said he remembered very well the workshop at the first WFH Global Forum in 2000, when participants from developing countries expressed frustration at the amount of discarded plasma in developed countries and discussed the notion of exporting unused cryo-paste to provide safe treatment to the developing world. It seemed like a very simple idea but there were many years of hard work on logistical, regulatory, legal, and marketing challenges. This issue has been looked at outside of the hemophilia community in recent years; for example, there is a section on global utilization of unused plasma in the Dublin Consensus Statement 2012 on optimized supply of plasma-derived medicinal products. The achievement of Project Recovery is a proof of principle that shows how unused plasma not required nationally can be turned into treatment for patients in developing countries lacking access to safe blood products.

A participant noted that it has taken 13 years to realize this project—how long will it take to implement in other places? What does cost-neutral mean and how is this being achieved? In addition, has the WFH considered seeking support from foundations or philanthropic organizations to expand Project Recovery, outlining the cost-neutrality alongside the humanitarian benefits as leverage for support? David Page said there are parties who are very interested in initiating a similar effort in Italy and Canadian Blood Services will collaborate with WFH to lend their expertise. Hereon, such efforts will take much less time. Cost-neutrality was a component of the project from the beginning and throughout the whole process, cost never arose as an issue or obstacle.

Such a project requires some initial investment and Biotest is bearing the initial costs, said Svenja Barckhausen. Cost-neutral does not mean there aren't costs and expenses to be covered, but in the long-term the initiative will be cost-neutral. Biotest will keep a share of the FVIII product to cover its initial costs and other costs. For example, Biotest will bear the costs of harvesting, transportation, and manufacturing. If this is to be a precedent for other countries, it is important to be aware that it will require some effort, especially on the part of the fractionator—support and commitment from top management is essential, she said. David Page noted that Biotest invested money and resources into Project Recovery without any guarantee that it would ever get off the ground. Ian Mumford said cost was not a consideration at all for Canadian Blood Services, which was prepared to invest resources and its regulatory know-how upfront and on an ongoing basis.

Over the past 13 years, the WFH did develop several funding proposals submitted to organizations such the Gates Foundation and the World Health Organization, and a range of potential partners, said Mark Skinner. One of the barriers was that patients with hemophilia and other bleeding disorders were too small of a niche population and the project did not fit within their broader organizational missions; there was also the issue of who would fund start-up costs. The pivotal turning point came when Biotest stepped forward and agreed to cover all the front-end costs, which allowed Project Recovery to really get underway. A number of other countries have since approached the WFH about initiating similar projects, including Italy, Australia, and some of the Nordic countries. The pilot project has involved unique challenges and decisions, therefore, it is important to complete the project and prove the principle before extending it to other countries, Mr. Skinner said.

It is important to promote Project Recovery beyond the bleeding disorders community, to inform and motivate blood donors to give blood, said Dr. Marijke van den Berg of the University Hospital of Utrecht in the Netherlands. David Page agreed and said there will be other opportunities to publicize Project Recovery, such as when the first vial is produced. The target date for the first infusion with the new product, Haemoctin®, is the WFH 2014 World Congress in Melbourne, Australia.

Point/Counterpoint: The Future of Plasma vs. Recombinant

This debate on the future of plasma-derived and recombinant products looked at challenges and opportunities for the global plasma industry in view of current developments in the recombinant field, particularly the new recombinant factor products expected to enter the market in the next few years.

In view of new developments in the field of recombinant clotting factor concentrates, do you think that plasma-derived clotting factor concentrates will:

Continue to play the same role	16%
Have a greater contribution in developing countries	51%
Have decreasing contribution both in developed and developing countries	32%
Don't know	1%

Future of Plasma Fractionation: A Pessimistic View

MAGDY EL EKIABY, MD, WFH VICE PRESIDENT COMMUNICATIONS AND PUBLIC POLICY

The challenges of plasma for fractionation are inherently due to the raw material itself, human plasma, said Dr. Magdy El Ekiaby. Source and recovered plasma collection, testing, and storage arguably present the biggest challenges, more so than cold chain transport and fractionation. Over the last three decades, the production and quality of factor concentrates have reached a very high level of safety and efficacy. Competent regulatory authorities as well as an array of legislations supporting blood collection activities, storage, manufacture, and cross-border movement of raw material and finished products have been key to ensuring the high safety of blood products available today.

According to the WHO Global Database on Blood Safety Summary Report 2011, about 92 million blood donations are collected annually. About half of these donations are collected in high-income countries, which represent 15% of the global population. In 39 countries, blood donations are still not routinely tested for transfusion-transmissible infections. Only 31% of the blood collected in low-income countries is separated and processed into blood components; thus the capacity of these countries to provide patients with the different blood components they require is still limited. The current reality is that recovered plasma for fractionation is mainly provided by the developed world.

The plasma industry also faces demographic challenges in developed countries. A progressive increase in aging in EU countries, even when compensated by immigration from other countries, will reduce the donor population. Changes in global travel patterns and trends, including a great increase in international travel and extended travel by young people to geographic areas where certain pathogens are endemic, also affect blood donations and the donor base as travellers are temporarily deferred from blood donation. The threat of emerging pathogens, such as variant Creutzfeldt-Jakob disease in the U.K. which led to the banning of U.K. plasma, is an ever-present risk. In addition, the concept of national self-sufficiency of plasma in European countries and relying solely on plasma collected domestically is slowly becoming history. Norway, which achieved self-sufficiency in blood and plasma products in the early 1980s, was the last to be self-sufficient, until around 2008 when immunoglobulin consumption reached a level that could no longer be sustained with solely Norwegian fresh-frozen plasma as a source.

There are also demographic and epidemiologic challenges in the developing world. The majority of blood donors in developing countries are family replacement donors and first-time donors; there does not exist a culture of repeat, regular blood donation. In addition, the high prevalence of transfusion-transmissible infectious diseases in developing countries is such that even when NAT blood screening is implemented, there are still high residual risks due to the high incidence of cases.

Currently, 69% of blood collected in low-income countries is used unmodified as whole blood for medical emergencies and not processed into components. The countries that do process blood donations into components mostly tend to discard the plasma. A lot of work would need to be done to process these blood donations and qualify its plasma for fractionation; donations would need to be tested according to international standards, processed into components, and the plasma further processed into safe plasma products that meet with all the regulatory requirements.

North America has shown that the solution is in source plasma—plasma collected from donors by plasmapheresis, for the purpose of fractionation into plasma products. Despite European resistance for some time, it is now becoming clear that the European countries cannot achieve self-sufficiency with only recovered plasma collected from their own national blood transfusion services, which in the last decade have started to switch to source plasma for fractionation collected from EU countries and/or imported from the U.S. The reality is changing and the notion of self-sufficiency, the original impetus for plasma fractionation domestically, is being relinquished.

The majority of source plasma for fractionation is obtained from paid donors, which raises ethical challenges. The WHO, International Society of Blood Transfusion (ISBT), and International Federation of Blood Donor Organizations (IFBDO) all advocate and promote voluntary, non-remunerated blood donors. Among its statutory goals, the IFBDO aims to combat all forms of marketing and gain with respect to blood and blood derivatives, under the principle that the human body is unalienable. Plasma as a raw material is a permanent challenge and its collection is not easy; this may be the single, main limiting point for the progression of plasma fractionation in the other parts of the world.

According to the 2010 WFH Global Survey, global FVIII consumption that year was 5.6 billion IUs (approximately 44% plasma-derived and 56% recombinant). Almost 60% of the global FVIII supply was consumed by nine countries: Australia, Canada, USA, U.K., France, Germany, Switzerland, Japan, and South Korea. Recombinant FVIII represents almost 80% of factor consumption in these countries and close to 90% of the global recombinant market.

The main consumers of recombinant factor concentrates are also the main producers of plasma for fractionation. This means there should be a surplus of plasma-derived factor concentrates available to developing countries at an affordable price—but the reality is that so far fractionators are not processing the unused cryo-paste in these countries, likely due to issues related to cost efficiency and the complexity of legal and regulatory requirements. Given the prevailing challenges in well-regulated countries, it will be even more difficult to initiate large plasma fractionation projects in developing countries, which would need to first develop extensive infrastructure for blood collection and processing before being able to consider plasma fractionation. The WFH's Project Recovery provides a model for moving forward.

It is important to remember the global disparities in availability of factor concentrates and access to treatment, and continue to use science and technology to advance improved safety of the products currently used in developing countries, as in the development of solvent detergent virally inactivated cryoprecipitate, and to make available safe and affordable biosimilars of current therapies.

New treatment products soon to enter the market will change the landscape and management of care for patients with inherited bleeding disorders. The long-acting factor concentrates will offer substantially enhanced efficacy and extended half-life based on various strategies such as pegylation, fusion technologies, and modification of amino acid sequences. Alternative therapeutic strategies such as tissue factor pathway inhibitors, activated protein C and antithrombin inhibitors, and bispecific antibodies against activated factor IX and factor X will help increase hemostatic efficiency. In addition, gene transfer research continues to advance and it seems increasingly possible that a hemophilia cure through gene therapy could become a reality.

Long-acting factor concentrates are expected to reach markets in the next few years. It may become possible for hemophilia patients, particularly in the nine countries that consume 60% of the global factor supply, to use the new products to embark on prophylaxis with less frequent infusions and even aim for 10-15% trough levels in hopes of a bleed-free world. As new state-of-the-art therapies become available, it is logical to expect global manufacturers, in the not too distant future thereafter, to transfer current recombinant technologies to major consumer markets in emerging countries such as Brazil, Russia, India, and China. In such a scenario, these countries could become self-sufficient in plasma fractionation and also serve regional markets at affordable prices. Data from the Plasma Protein Therapeutics Association on the economics of plasma production indicate that raw materials (i.e., plasma) and direct manufacturing typically represent about 60% of the cost base for plasma-derived products. The cost of raw materials cannot be reduced but there is a good margin for price reduction by manufacturing in developing countries where labour costs are much lower than in the developed world.

In developing countries, treatment is constantly constrained by scarcity of treatment products; the majority of patients with hemophilia do not receive adequate care due to the limited availability and high cost of factor concentrates. The introduction of new products presents an opportunity to accelerate global access. Payers generally expect that the optimization, innovation, and efficiencies achieved in manufacturing will be passed on in product pricing, but given the array of new products coming to market, one can still hope that market competition will help keep prices down.

To enhance affordability and supply, it is time for a new paradigm in the 21st century based on the substantial unmet global demand. With today's recombinant technology capabilities and many new products coming to market, supply constraints should not be a factor. Manufacturers should evolve their business development, production, marketing, and pricing strategies to adapt to the global reality. A new business model based on high volumes and low margins should be pursued, in recognition that much more product is needed globally, and were it to be made available, demand would increase as more and more patients are treated. For the foreseeable future, the definition of optimal treatment may vary based on the economic capacity of a country, or be only incrementally achievable. However, there is no doubt that the technology, knowledge, and capacity exist to dramatically improve global access.

The plasma fractionation industry has played a major role in providing safe and effective medicines over the last three decades. Progressive innovations, particularly in recombinant technology, are currently complementary to fractionated plasma products. However, the new generation of technologies may well come to prevail in the next two decades, particularly as advances in gene and stem cell therapies may come to provide safer and permanent alternatives to fractionated plasma products in the future.

The Global Plasma Industry: An Optimistic Future

PIERRE-FRANÇOIS FALCOU, MD, EXMBA, ALLIANCES DIRECTOR, LFB BIOMÉDICAMENTS, FRANCE

Dr. Pierre-François Falcou recounted that when he joined the plasma fractionation industry in 1996, a few years after the introduction of recombinant FVIII concentrates, there was a sense that plasma-derived concentrates could soon be rid from the landscape—yet after all these years, the industry is still here. At the time, FVIII concentrate was the driving product of the plasma industry. However, the drivers of demand have changed; demand for albumin led the industry for a short period but intravenous immunoglobulin (IVIG) has emerged as the driving product and will likely continue to drive plasma manufacturers for many years. His presentation focused on the strategic drivers of the industry and how they signify an optimistic future for the plasma industry.

There are numerous factors currently contributing to market growth: population aging, untreated patients, economic models for costing in the global FVIII industry, market capping of listed companies, prices in the U.S., barriers to entry, and manufacturing productivity. The current trend in the global plasma industry is increasing growth in manufacturing scale, automation, and production. In recent years, major plasma manufacturers such as Baxter, CSL Behring, and Grifols have expanded their fractionation capacities and increased production volumes. The global plasma market is substantial and worldwide demand continues to increase.

Plasma Availability

The reality is that plasma is a limited resource. The United States currently produces about 70% of the global plasma supply, through a dual system that relies largely on the collection of source plasma from paid donors but includes recovered plasma from voluntary unpaid donors. Some emerging countries have domestic fractionation capacity but still need some imported starting plasma or plasma products, and therefore are not yet able or ready to contribute to the global plasma supply. Yet the global market and demand for plasma products continues to grow annually.

The global plasma industry, regulators, and other stakeholders need to move beyond the debate on paid vs. paid blood donors and develop a strategy based on longer-term projections on worldwide demand, for example, five to ten years rather than annual projections, to enable blood collection and plasma manufacturers to plan accordingly to meet the needs of the global population.

Industry Landscape

The competitive landscape is directly linked to patient demand for plasma-derived products, choice of treatment, and access to care. Due to regulatory requirements and infrastructure and manufacturing costs, the plasma industry needs to achieve economies of scale—increased production and output allow manufacturers to reduce variable costs, improve profitability, and amortize investment costs. In terms of industrial capacity, manufacturers have extendable fractionation capacities that make them capable of responding to market growth and demand for greater supply, at least to the extent of plasma availability.

Over the past decade, there have been a number of mergers and acquisitions in the plasma industry. Consolidation has been driven by cost pressures and efforts by manufacturers to rationalize operations. It is important to try to keep the market open and, therefore, to be watchful over the landscape as further consolidation could reduce treatment choices. At the same time, it is important to appreciate that consolidation allows manufacturers to combine resources to address safety issues, improve production capacity, control expenses, and adjust product prices. Consolidation is also a way to keep the industry long-lasting and profitable.

A number of developing countries—Mexico, Brazil, Saudi Arabia, India, and Malaysia— are currently looking to establish domestic fractionation capacity. This will allow plasma that is not yet used to be evaluated. The newcomers will be able to challenge the manufacturers based in the developed world; this will contribute to the future of the global plasma industry by raising benchmarks and competition.

Market Access

Regulators play an extremely important role in the plasma industry because they assure blood safety and the quality of blood products, and control market access. Moving forward, with many new and enhanced products in development, regulators and industry need to work together to try advance product access and innovation.

The plasma industry continues to pursue very strong investment policies and the global market will continue to grow for some years with IVIG as the main driver. The barriers to market entry put in place by the developed world in terms of regulatory requirements on quality, treatment efficiency, production, and marketing help maintain and protect the industry from external challenges.

Proteins

There are several types of fractionated products currently driving the plasma industry: albumin, IVIG, and factor concentrates, among others. Factor concentrates have had a long-lasting presence on the market but is no long a market driver. However, while it is true that recombinant products, biosimilars, and gene therapy will affect the global plasma market, these active proteins have specificities that the recombinant industry may find difficult to reproduce or change.

Albumin

Albumin is a plasma protein used in critical care and as a stabilizer in factor concentrates and other pharmaceutical formulations. It was the first plasma product developed using the fractionation process. In the early 2000s, there were concerns about the relative safety and efficacy of albumin compared to starches but these were subsequently dispelled. The plasma industry has a lot of investment in proving that albumin has extremely complex and rich properties and pharmacological effects. While no longer a main driver, global demand for albumin continues to contribute to the global plasma industry's costing equation and has an impact on the amount of source plasma collected.

Intravenous Immunoglobulin

IVIG is an intravenous blood product that contains immunoglobulin G (IgG). There are two major fields for IVIG, primary immune deficiencies and autoimmune diseases. These fields encompass a wide diversity of diseases, and the need will protect the plasma market from the new recombinant, biosimilar, and gene therapies for a while. IVIG is the industry driver at all levels. It is approved to treat a range of autoimmune, infectious, and idiopathic diseases, and new indications are not exhausted. In France, physicians use IVIG to treat idiopathic thrombocytopenic purpura, myeloma or chronic lymphocytic leukemia, Guillain-Barré syndrome, Kawasaki disease, and others. IVIG is also used off-label for dozens of other diseases, some of which appear well-suited to IVIG; however, as yet, indications have not been proven.

Alpha 1 antitrypsin

Alpha 1 antitrypsin (A1AT) deficiency is a genetic disorder that can cause lung and liver disease. Treatment with the A1AT protein is very well-established in North America and several countries in Europe. At present, many patients remain undiagnosed and untreated. Although development of a recombinant alternative is being explored, good market conditions can be expected for A1AT in the next several years.

Fibrinogen
Fibrinogen concentrate is currently manufactured by a limited number of companies, though other manufacturers are working to develop their own compounds. Fibrinogen concentrate is used for surgery, childbirth, or post-partum hemorrhage, and other bleeding trauma. It is available in a number of countries in Europe and other parts of the world, and can be expected to assume growing importance in critical care. Fibrinogen is an opportunity for economic leverage of IVIG production.

Factor VIII
Although the market for plasma-derived factor concentrates faces some challenges, the future is bright. The worldwide market for FVIII concentrates in 2011 was 8 billion IUs. As hemophilia shifts from a standard of 1 IU per capita to a new standard of 2 IU per capita as the minimum acceptable level of treatment, demand will increase. The question is how long it will take for the recombinant industry to make available 2 IU per capita worldwide at affordable prices. The long-acting recombinant factor concentrates will increase competition with the plasma-derived industry but the real challenges will be the new recombinant products and gene therapy still to come.

Other interesting proteins that manufacturers are working to develop include: inter alpha antitrypsin, ADAMTS 13, factor H, transferrin, IgM, hyperimmune Ig, and factor V.

Discussion

The plasma industry is not going to disappear with the arrival of new recombinant products for the simple reason that the industry does not depend on the presence or absence of alternatives to plasma-derived factor concentrates, said Albert Farrugia. The primary driver of the plasma industry is IVIG and the actual current therapeutic demand for IVIG exceeds the current plasma capacity of the world. Irrespective of whether plasma or recombinant will be the way forward, a lot of plasma is being collected in the world for necessary treatments. Accessing the FVIII that is available in the world seems reasonable if the economics are right, but it is not reasonable to pitch plasma extraction from blood collected for red cell concentrate. As Dr. El Ekiaby noted, most of the blood collected in developing countries is used as whole blood; in other words, the blood transfusion needs of the emerging world are not to separate plasma from red cells to produce red cell concentrate in order to derive plasma for the fractionation industry. As Dr. Falcou mentioned, fibrinogen concentrate is quite promising and achievable. Fibrinogen concentrate is primarily needed because red cell transfusions are deficient in fibrinogen due to the lack of plasma.

Dr. Alok Srivastava said one concern is whether the cost per unit of plasma-derived factor concentrates will be affected as safety constraints increase year by year; whereas with recombinant concentrates, manufacturing is a matter of capacity once the methodology is established. He anticipated that recombinant costs will decrease substantially, while plasma production costs could remain steady or rise. The price per unit is what will ultimately determine which type of factor product gets used. Dr. Falcou said whether manufacturing plasma or recombinant products, downstream purification processing requires chromatography, safety controls, etc.; economically, there will be convergence on the same minimum costs. At the end of the day, recombinant and plasma-derived products will be sold at the same price based on manufacturing marginal cost plus margin. The question is whether emerging countries will be able to afford the treatment sold at this price.

Brian O'Mahony said in recent years, there has been an assumption that IVIG would become a licensed indication for Alzheimer's which would lead to a dramatic increase in demand and in turn possibly lead to better plasma collection and a greater supply of plasma products such as factor

concentrates at a lower cost. That now seems much less likely. With the longer-acting recombinant factors coming on the market, it's quite likely that recombinant products will start to drop in price. What will happen in relation to the marketing and pricing of plasma-derived products? Regardless of Alzheimer's, the indications and new indications of IVIG are substantial enough that demand in the developed world will fuel this industry, Dr. Falcou said. He anticipated recombinant and plasma-derived factor concentrates will be sold at the same price, which is the downstream marginal cost plus margin.

Prof. Farrugia said there is more than enough need for IVIG with the established indications for primary immunodeficiencies, autoimmune diseases, and acute infections, even without Alzheimer's or emerging and off-label indications. The downstream costs are definitely important but it is important not to forget the upstream costs—the cost of the raw material for plasma fractionation. There will always have to be a floor price for plasma-derived factor products because of the costs of infrastructure to collect plasma, ensure pathogen safety, and adhere to good manufacturing practice. The question is how the economics balance out. Commonality on costs downstream does not mean that the price will be the same.

Dr. El Ekiaby said the plasma industry needs to adopt a forward-looking and innovative approach to truly address the global issues related to access and affordability and satisfy the global demand for factor concentrates. The audience was polled again to assess whether their views on the future of plasma-derived and recombinant concentrates had changed as a result of the presentations.

In view of new developments in the field of recombinant clotting factor concentrates, do you think that plasma-derived clotting factor concentrates will:

Continue to play the same role	16%
Have a greater contribution in developing countries	51%
Have decreasing contribution both in developed and developing countries	32%
Don't know	1%

SESSION 2: CLINICAL AND ECONOMIC ASPECTS OF NOVEL TREATMENT PRODUCTS

ALOK SRIVASTAVA, MD, VICE PRESIDENT MEDICAL, WORLD FEDERATION OF HEMOPHILIA

This session explored current issues and developments related to clinical practice and the continual aim to improve treatment efficacy and health outcomes for patients with bleeding disorders. Recent studies were presented on the limitations of the annual bleed rate in managing hemophilia due to subclinical bleeding which causes incipient joint damage, and the beneficial role of early prophylaxis in the prevention of joint bleeding and hemophilic arthropathy. The session also looked at clinical aspects of novel treatment products and the potential for improved, individualized care through new treatment paradigms based on higher trough levels and pharmacokinetics, as well as economic considerations such as pricing, sustainability, access, and increased supply. The final presentation focused on the rise of the patient voice and the critical importance of patient engagement, patient-centred care and shared decision-making in clinical development and health care.

The definition of primary prophylaxis, as suggested by the ISTH SSC, is initiation of prophylaxis:

Before the first bleed	40%
After the first bleed but before the second bleed	47%
Before clinical joint damage	11%
Before radiological joint damage	2%

Under ideal conditions, with current clotting factor concentrates, in patients receiving prophylaxis you will aim for:

Annual bleed rate of <1	20%
Annual bleed rate of <3	15%
Factor level of >1% at all times	29%
Annual bleed rate of <1 and factor level of >1% at all times	36%

In practice conditions, most children in Western Europe start prophylaxis after the:

First bleed	47%
Second bleed	30%
Fifth bleed	18%
Tenth bleed	5%

With the possibility of using long acting factor concentrates, would you aim for a target trough level of:

>1%	22%
>3%	32%
>5%	22%
>10%	24%

The main determinant of what target trough levels to aim for in prophylaxis with long-acting products will be:

Long-term data showing safety and superiority of higher levels	37%
Availability and access to products	19%
Patient preferences	13%
Cost-benefit analysis	31%

Is the Annual Bleed Rate Enough? The Micropathology of Joints

MARILYN MANCO-JOHNSON, MD, PEDIATRIC HEMATOLOGIST, HEMOPHILIA AND THROMBOSIS CENTER, THE CHILDREN'S HOSPITAL, DENVER, COLORADO, USA

Patient monitoring of number of bleeding episodes per year, called the annual bleed rate, along with physician follow-up are important aspects of managing hemophilia. Dr. Marilyn Manco-Johnson described the micropathology of joints and results from four studies: the Joint Outcome Study, the CDC Universal Data Collection Project, meta-analysis of MRI studies of hemophilia, and the Joint Outcome Continuation Study. The evidence suggests that number of clinically determined joint bleeds may not completely account for the hemophilic arthropathy seen structurally.

The classic clinical diagnosis of joint bleeding is physical and external. The patient reports a tingling, warmth, or pain sensation, and a physical exam finds decreased range of motion of the joint, swelling, and external warmth. More recently, clinical assessment has been augmented by pathophysiological assessment of a joint bleed. Imaging technology for acute joint bleeds reveal fluid accumulation in the joint, hemosiderin deposition into the synovium (evidence of bleeding), and synovial thickening. Hematologists are also studying molecular and histologic evidence of joint bleeds such as expression of proliferative and inflammatory cellular markers, including ligands and alteration of bone and cartilage activity, and osteoblastic and osteoclastic activity.

Hemophilic arthropathy is classically identified by a physical exam that includes fixed flexion and extension contractures, muscle atrophy and weakness, bony outgrowth, and joint instability. With imaging technology, anatomical markers have been added including subchondral erosions, bone cysts, cartilage narrowing and loss, and osteoporosis.

Several studies have demonstrated evidence relating the annualized bleeding rate to hemophilic arthropathy. The five-year prospective Orthopedic Outcome Study followed 477 males with hemophilia, age 6 through adulthood; 66 patients were on prophylaxis and 411 patients were treated on demand. The patients on prophylaxis had on average 10 bleeding episodes, with a 1% increase in their WFH physical exam joint scores annually. The on-demand patients had on average about 25 clinical bleeds per year and a 3% annual increase in their physical exam joint scores. A smaller study on arthropathy and secondary prophylaxis to prevent joint deterioration showed that in a group of 13 boys, ages 2 to 12, who all together had 16 affected joints, eight boys improved in physical function, four stabilized, and only one had progressive joint deterioration. WFH physical exam joint scores can improve and X-ray scores may stabilize when clinical bleeding rate is decreased.

Dr. Manco-Johnson discussed evidence from four studies which suggest that clinically determined joint bleeds may not completely account for arthropathy.

Joint Outcome Study (1995-2005)

The Joint Outcome Study was a randomized clinical trial funded by the U.S. Centers for Disease Control and Prevention (CDC) which enrolled 65 boys with severe hemophilia A in two arms: prophylaxis with routine infusions of FVIII (25 IU/kg) every other day, or an enhanced episodic protocol (augmentation of standard on-demand therapy using 3 or more infusions per joint bleed). Enrolment and treatment had to be initiated before 30 months of age. Outcome was determined at age 6. The primary outcome was joint structure determined by MRI of the six index joints (both elbows, knees and ankles), and the secondary outcomes were joint bleeding events clinically determined by physical examination of joint function, total number of joint and arterial bleeding events, and factor utilization. The primary finding of this study was the proportion of children at

age 6 with no osteochondral defects detected by MRI of the elbows, knees and ankles; 58% of the boys on episodic therapy and 93% of the boys on prophylaxis maintained anatomically normal joint cartilage. Compared to prophylaxis, the relative risk for joint damage for patients on the enhanced episodic therapy was sixfold that for patients on prophylaxis. Prophylaxis provided an 84% risk reduction in structural bone disease.

The clinical study showed wide evidence of variable susceptibility to bone and cartilage damage from bleeding. Analysis of the number of index joint bleeds and the mean MRI score found there were boys who had numerous joint bleeds but showed no damage by MRI, and there were boys with bone and cartilage damage who had not had clinically recognized bleeding. The MRI outcomes showed a very modest correlation between joint damage and number of clinical joint bleeds. MRI evidence of osteochondral defects and bone and cartilage changes are only partially explained by the number of clinically evident bleeding events, and osteochondral defects in the absence of overt bleeding are primarily seen in children on episodic therapy. The investigators posited that the abnormal MRI findings could be due to microbleeding or oozing into joints of patients on episodic therapy and that prophylaxis might interrupt microbleeding. There may also be other effects of FVIII deficiency on metabolism, cartilage and bone matrix, osteoclastic and osteoblastic activity, and inflammation.

CDC Universal Data Collection Project (1998-2010)

This surveillance initiative was funded by the CDC and implemented through the U.S. Hemophilia Treatment Center Network, a collective of 130 hemophilia centres. The treatment centres collected serial data on 26,614 visits by 6,194 males with severe hemophilia A over 12 years. Data was collected on bleeding rates, indicators of arthropathy including joint range of motion, and other outcomes. Analyses were made of arthropathy, as indicated by percentage loss of joint range of motion, in comparison to various clinical factors. Repeated measures were taken of overall joint range of motion in 3,368 boys with hemophilia, ages 2 to 19.

The data showed that joint range of motion correlated negatively with increasing bleeds, and range of motion decreased as participants got older. There was no correlation with either primary or secondary prophylaxis. A longitudinal logistic regression was then carried out to look at changes over time. Obesity was found to strongly correlate with decreased range of motion. Patients who were not on primary prophylaxis had progressive loss of range of motion, whereas patients on secondary prophylaxis had significant but lesser change in range of motion over time.

Interpretation of the data is complex. In this registry, most participants on primary prophylaxis were in the early years of life; joint range of motion was preserved in both young patients on prophylaxis and young patients on episodic therapy and there was no statistical difference yet seen between the two groups. The factors significant in predicting decreased joint range of motion include increasing age, positive inhibitor status, and more frequent bleeding episodes.

Data from serial evaluations of joint range of motion show that joint preservation was highly associated with primary prophylaxis, and significant with secondary prophylaxis. The data suggests that preservation of joint function in severe hemophilia, as measured by joint range of motion, is most highly correlated with primary prophylaxis, which has two possible mechanisms of action; prevention of clinical episodes of joint bleeding at an early age, or routine replacement of FVIII from an early age.

Meta-analysis of MRI studies of joints in hemophilia (2011-2014)

The meta-analysis of MRI studies of joints in hemophilia is funded by the CDC. It includes data from three studies involving patients with severe hemophilia who had joint MRIs taken in clinical data. The data from each individual was aggregated in a single database for meta-analysis. For continuous patient meta-analysis, only data elements common to all three databases could be used.

The MRI and WFH physical exam scores were converted to a single scale developed through the International Prophylaxis Study Group. The data was analysed by total patient score and individual joint score. The analyses segregated patients treated only on demand from patients on prophylaxis. Analysis of patients treated only on demand found no significant correlation between total patient MRI score and annualized bleeding rate, i.e., annualized bleeding rate does not predict joint outcome in hemophilia A patients treated on demand.

Joint Outcome Continuation Study 2009-2017

The original 65 participants in the Joint Outcome Study are being invited back to a continuation study, to follow up on their treatment after age 6 and until age 18. About half of the potential participants have been involved in this study. Almost all of the children on the early prophylaxis arm had elected to remain on prophylaxis, and most children on the enhanced episodic arm had adopted prophylaxis when study results were disclosed. The data includes infusion logs from birth, joint physical exams, quality of life assessment, and MRIs taken every four years until age 18 as part of the follow-up study. Participants at the first follow-up evaluation had a mean age of 13.

The aim of this observational study is to determine the natural history of joint development in hemophilia and the impact of primary and secondary prophylaxis on the prevention, limitation, or reversal of hemophilic arthropathy. The study data shows higher MRI scores with higher bleeding scores, and lower MRI scores in patients who had been on early prophylaxis.

The annualized bleed rate is unquestionably important. However, clinical joint bleeds in the annualized bleed rate account for only some of the structural joint damage detected by MRI in patients with severe hemophilia. Prophylaxis mitigates some of the damage, though mitigation may be primarily in patients with non-clinical or micro-bleeding. This data alters the conversation around individually tailored prophylaxis, insofar as it suggests that not all clinically important bleeding events can be clinically appreciated. Routine FVIII replacement provides a beneficial effect, as the presence of FVIII, even in the absence of clinical bleeding, conveys some protection against joint bleeding and hemophilic arthropathy.

Discussion

The presentation showed that joint preservation and the prevention of arthropathy is linked to early prophylaxis and that clinical bleeding does not explain all of the osteochondral defects detected by MRI, said Dr. Flora Peyvandi. She suggested looking at data on the ages at which children had their early bleeds because the bleeding process is different later on. Data on the first two to five bleeds could yield new information.

There is now convincing data that prophylaxis is superior to episodic treatment, said Dr. Alok Srivastava. The current target is at least 1% trough level to prevent joint bleeds; a large number of children entering adolescence maintain near normal joints but a certain number have signs of joint damage even without recording clinical bleeds. The goal of prophylaxis is to maintain factor levels above 1% but this may or may not be achieved all the time. Dr. Manco-Johnson said most of the

abnormalities seen in individuals on early, continued prophylaxis were minor, such as excess fluid accumulation in the joint and hemosiderin deposition into the synovium. Individuals on prophylaxis did have joint bleeds throughout childhood, but did not seem to have any severe bone and cartilage impacts.

Dr. Srivastava said if the current paradigm of maintaining a trough level of at least 1% is considered successful for maintaining normal joints, what is the rationale for pushing for a higher trough level of 3%, 5%, or 10%, as currently being debated? In spite of having a paradigm based on a 1% trough level, there are people who are getting a certain amount of joint damage. Until now, treaters have been constrained by the half-life of the current factor products, which did not allow the option of aiming for higher trough levels. Now that the option is available, is there justification to aim for higher trough levels?

There are several age-related reasons to support tailoring prophylaxis, Dr. Manco-Johnson said. First, some young children or even older children and adults have spontaneous joint hemorrhages at 1-3% trough levels, so they do need higher levels such as 5% to prevent bleeding. Second, with very young children, parents cannot always tell when a joint bleed is beginning and whether there is a higher risk for joint bleeds; the clinical way to deal with this is to raise the trough level. Third, young children developmentally do not have a concept of rest and its importance to healing from a bleed. A study presented at a meeting of the American Society of Hematology two years ago showed that young children used more factor to treat bleeds and for a longer duration than older patients.

The annual bleed rate is not proportional to joint damage and cannot be relied upon to predict joint damage because there may be subclinical bleeds that affect the joints, Dr. Magdy El Ekiaby said. There are different rates of bleeding, possibly due to different clearance rates of FVIII from the bloodstream or even individual physical behaviour and activity levels. Prophylaxis that is tailored for individual patients could address some of these issues.

Dr. Manco-Johnson said it is not really possible to have no bleeding—prophylaxis is a balance of providing the best care for patients with hemophilia and allowing them to live a full life, to engage in activities and sports, and risk some injuries. Therefore, the goal should be no preventable bleeds because it is not possible to completely avoid injury and bleeding.

Changing Treatment Paradigms – What Should Personalized Care Look Like?

STEVEN W. PIPE, MD, UNIVERSITY OF MICHIGAN C.S. MOTT CHILDREN'S HOSPITAL, ANN ARBOR, USA

Over the last 10 years, advances in science and new technologies have begun to make it possible to tailor medical decisions to individual genetic and molecular profiles and other predictive factors. Dr. Steven Pipe spoke about changing treatment paradigms in hemophilia, particularly as long-acting factor therapies enter the market, and how prophylaxis could be individualized in order to provide optimal care to patients.

Comprehensive Hemophilia Care

Comprehensive hemophilia care is a multidisciplinary approach that focuses on treatment and prevention of acute and chronic bleeding, and, equally important, advancing health-related quality of life parameters so that people with hemophilia can fulfill normal academic, social, and vocational roles. Over the past 40 years, the comprehensive care model has led to significant advances in treatment and care for people with hemophilia, resulting in substantially improved health and musculoskeletal outcomes, reduced morbidity and mortality, and better quality of life. Where resources are available, the goal of hemophilia treatment extends beyond on-demand factor replacement therapy to the prevention of bleeds through prophylaxis so that people with hemophilia can live normal lives.

Prophylaxis regimens vary considerably worldwide but for many years the goal has generally been to maintain a baseline factor level, or trough level, above 1% to prevent bleeding into the joints, one of the main complications of hemophilia. Current debate has focused on whether 1% is sufficient to prevent bleeding, and whether higher trough levels are actually needed to achieve the absence of bleeds, which is the ultimate curative goal. A recent study showed that absence of joint bleeding might only be reached when approaching FVIII trough levels of 15%. In practice, there will be varying targets and different reasons why specific approaches are adopted for individual patients.

Tailored Therapy

Tailored therapy aims to improve efficacy and outcomes for individual patients by optimizing therapy based on their specific characteristics such as phenotype, genotype, and treatment response. There is considerable phenotypic variation in the hemophilia population. A variety of factors affect phenotypic expression. Genotype plays a contributing role; however, a recent RODIN study found that FVIII mutation accounts for only part of the significant phenotypic variability among patients with severe hemophilia A. Inflammatory genes influence response to bleeds and may be important in the manifestation of consequent joint disease. In addition, there is also interesting data on age at first joint bleed, clotting factor consumption in relation to age at first bleed, and joint health scores as patients grow older.

Hemophilia therapy is already tailored to some extent in that oftentimes clinicians might use one common prophylaxis approach for their hemophilia patients, but the individual regimens will vary from patient to patient. The Canadian escalating prophylaxis study starts patients on a low-dose regimen to reveal phenotypic differences between patients then escalates therapy to avoid joint bleeding; breakthrough bleeding is the trigger for advancement to the next level of replacement therapy. However, recent data from the study shows that the longer patients were on the tailored therapy, the more evidence there was of joint damage, as seen in all major joints at different age points of evaluation. Therefore, there can be both benefits and consequences to tailoring therapy.

Long-Acting Factor Products

The long-acting factor concentrates coming into the market will impact how clinicians deliver care. Prolonged half-life will result in fewer infusions per week, month and year, and fewer peak trough levels per week, month and year. Clinical trial data shows that glyco-pegylated FIX will allow long intervals from infusion to time to 1%, the baseline factor level for prophylaxis, and that the time interval can be further extended by increasing dose. Higher efficacy will allow infusion strategies to be adjusted to target other thresholds, such 3%, within very manageable intervals. A patient who currently infuses factor twice a week could be able to infuse long-acting factor once a week and re-dose in the 10-30% range. The higher the factor level, the less likely a patient will have joint bleeds and joint damage later in life. There is data that suggests a 10-15% factor level is needed to achieve an absence of joint bleeds.

Factor Trough Levels

It has been well established that there is an increased likelihood of breakthrough bleeding with the more time spent below the 1% trough level, and that patients on the same fixed dose regimen display variable half-life and time to 1%. The Advate® prophylaxis clinical study evaluated the treatment efficacy of two prophylaxis regimens: standard prophylaxis (every second day) and pharmacokinetic-driven (every third day) prophylaxis, both targeted to maintain FVIII trough levels above 1%. Results showed a fourfold variation in half-life among patients and great variability in the dose required to keep individual patients above the 1% threshold; even though patients were anchored at 1%, their peak levels varied. In terms of the impact of treatment on bleeding rates, a comparison of the distribution of the average peaks to annualized bleed rates found that patients who had lower peaks had very long endogenous half-life; therefore, they did not need as high of a dose to anchor them to a 1% trough level and they accumulated more bleeds per year than those who required higher doses to reach a 1% trough level. Analysis of time spent above 20%, 30% and 40% factor levels showed a significant relationship with lower annualized bleed rate. Conversely, increased time spent in the lower range of 3-5% factor levels seemed to correlate with an increased risk for bleeding.

While a 1% target trough level would generally be effective, a single strategy cannot accommodate all the phenotypic variations in the hemophilia population. Some patients truly require alternative dosing regimens with higher doses and higher trough levels; for instance, a patient with a target joint may need a higher trough level to prevent breakthrough bleeding. The long-acting factor products will allow clinicians to achieve a higher trough level by tailoring the factor dose and infusion intervals. This will shift the treatment paradigm from basic factor replacement therapy to one that focuses on optimizing the use of long-acting factor products according to individual pharmacokinetics. To further advance hemophilia care, significant improvements are needed to even better control bleeding, preserve joint function, and reduce the burden of factor infusion.

Pharmacokinetic Modelling

Information and insight on individual pharmacokinetics would be very helpful to clinicians, and empowering to patients. The challenge is that measuring individual pharmacokinetics is very cumbersome because it requires intensive sampling. Individual pharmacokinetic assessments are rarely done outside of research studies. However, if a population pharmacokinetics formula were available, it would be possible for clinicians to obtain a small number of samples from a patient at several time points, use visual analog scale analysis to determine the patient's half-life, and establish an individualized formula for the patient.

As part of the home therapy component of comprehensive care, patients must keep treatment logs or diaries to record all their infusions and bleeds, and visit the hemophilia treatment centre for an assessment every six months. While this has been the standard of care, it is somewhat unsatisfactory

because bleeds occur in the window between visits and the lag-time in feedback could potentially lead to a lot of damage. The use of technologies such as electronic devices for logging bleeds and infusions now allows earlier intervention; clinicians can view the patient's data remotely in real-time, set up alerts if the patient has a breakthrough bleed or an unusual number of infusions, and intervene quickly rather than waiting until the next appointment at the clinic.

There already exist many health-related applications for smartphones including a variety of tools, instruments and calculators that address chronic conditions and in some cases advance medical adherence. A mobile healthcare app for hemophilia could potentially synthesize the knowledge on long-acting factor products with insight from population pharmacokinetics, enable clinicians to determine the pharmacokinetic profiles of individual patients and appropriate dosing regimens, and provide patients with real-time feedback and visual cues on their factor levels and pharmacokinetics so that they can better manage their care.

A number of groups and industry partners are currently working on the development of accessible software systems and these could be leveraged into mobile healthcare technologies. For example, a smartwatch could give patients access to information on the time of their last infusion, the dose, pharmacokinetics, and factor level at any precise moment. This will alter the hemophilia treatment paradigm, eliminate the six-month interval between assessments, and put all the decision-making on dosing, threshold, and infusion notifications in the hands of the patient and clinician.

Discussion

A bleeding disorders smartwatch is a great idea but won't work for 75% of people with hemophilia in parts of the world without access to basic treatment, let alone prophylaxis, a participant noted. In the U.S., Kaiser Permanente, a consortium of integrated healthcare services and insurance providers, is initiating a health incentive plan offering incentives to employees who participate in workplace wellness programs. There can be financial incentives to encourage participation such as gift cards, cash, lower insurance premiums, etc. Could such incentives be valuable in the hemophilia context to encourage patients to make healthy choices, adhere to treatment, and diligently manage their condition? For example, a financial incentive could be offered to get hemophilia patients to participate in pharmacokinetic studies.

Dr. Pipe said with an individual patient's pharmacokinetic profile, the clinician can determine the dose and treatment interval best suited to the patient. Health insurance companies that offer incentives such as insurance premium deductions for hemophilia patients who obtain pharmacokinetics assessments would likely be able to easily recoup the value of the financial incentives.

Dr. Flora Peyvandi said pharmacokinetic modelling would lead to a big improvement in the quality and utilization of treatment but expressed doubts about personalized treatment based on individual pharmacokinetics, given that hemophilia is a multifactorial disease and there are different factors that contribute to bleeding and clinical outcomes, not just factor level, which also need to be taken into account.

Thomas Sannié of l'Association française des hémophiles cautioned that not all patients will be keen to be monitored and checked by the hemophilia physician all of their lives. He also emphasized the importance of patient education, starting with the ability to be able to detect bleeds as soon as they start, and helping patients develop skills for dealing with the complications of hemophilia. Patient education and empowerment is critical, Dr. Pipe said. Moving forward, it is important to embrace the phenotypic variation in the hemophilia population and tailor treatment accordingly. Having a good

understanding of pharmacokinetics and precise data on their own individual profile (e.g., time of last infusion, dose, current factor level, etc.) will empower patients to take control of their care. Five years ago, the term "time to 1%" was not common but today pharmacokinetics is increasingly part of physician-patient discussions.

Economic Considerations: Pricing, Sustainability, Access, Increased Supply

ALBERT FARRUGIA, VICE PRESIDENT GLOBAL ACCESS, PLASMA PROTEIN THERAPEUTICS ASSOCIATION

Over the past 40 years, the treatment of hemophilia with factor concentrates has reduced morbidity and mortality and revolutionized quality of life and life expectancy for people with hemophilia. It is well known that higher factor usage per capita leads to superior outcomes, to the extent that people with hemophilia can engage in normal lives—this is why patients are seeking more and more access to treatment, Albert Farrugia said.

However, recent terminology in the field of hemophilia is worrisome such as: acceptable number of bleeds, adequate preservation of joint function, and the notion that prophylaxis should be started after the second joint bleed. "The acceptable frequency of bleeds is zero, adequate preservation of joint function should mean normal, and prophylaxis should be started at diagnosis. All the factors to the contrary are underpinned by simple economics," Prof. Farrugia said. He presented economic considerations and evolving perspectives on access to hemophilia treatment.

Treatment

Where available, treatment with factor concentrates has led to increased life expectancy. A 2007 U.K. study of survival rates among men with hemophilia who were not infected with HIV compared to the general male population in 1999 found that U.K. men with hemophilia are now approaching a normal life expectancy. However, a study published this year on incidence, mortality rates, and causes of deaths in hemophilia patients in Sweden found that people with hemophilia still have a lower life expectancy compared to the general population, primarily due to hemorrhage; 13% of deaths in hemophilia in Sweden are caused by hemorrhage. Data from a 2012 Italian study shows an increase in risk of intracranial hemorrhage relative to age; the risk is high in the early years of life, decreases during childhood and adulthood, then increases with age in the later years. There are large efforts looking at the question of lifelong prophylaxis treatment.

About 30 years ago, factor usage of 1 IU per capita became the standard. Recent studies have shown that a 1% trough level is clearly not adequate in terms of complete prevention of joint bleeds. A study by the Van Creveld Clinic in the Netherlands analysed the association of joint bleeds according to baseline FVIII activity levels and found that, overall, 15-20% FVIII activity levels are needed to adequately prevent bleeds. The data raises the question of whether all people with hemophilia are receiving inadequate treatment and whether the future for hemophilia may involve higher dosages.

Safety and Access

The hemophilia landscape has been changed by the perception of safety, due to the viral transmissions through blood products in the past, and the perception of costs based on recent economic realities. The concerns surrounding safety have given way to concerns about cost and access. "When people talk about the need to preserve product, tailor dosage and individualize treatment, it has a basis in good medicine, but at the back of their minds there is likely also the whole question of how much the product costs," Prof. Farrugia said.

With the advent of increasing types and quantities of FVIII, there is now enormous potential for the production of FVIII from both plasma-derived and recombinant sources. Data on FVIII demand collected by the Marketing Research Bureau shows that in 2010 about 3 billion IUs of plasma-derived FVIII concentrate were consumed. Prof. Farrugia estimated that in 2010 about 3,000 tonnes of plasma were fractionated and only about 50% of the plasma was used to extract FVIII. However, this was the same situation 30 years ago and is not necessarily reflective of so-called cryoprecipitate wastage. A lot of the plasma that is collected is not considered suitable for fractionation into FVIII according to regulatory and other requirements. The plasma industry today continues to grapple with the challenges and difficulties posed by limited availability of plasma, and seek ways to improve plasma factor levels and gain higher yields.

Recombinant factor became part of the paradigm and exerted its dominance on the landscape because it was developed primarily as a reaction to the safety issues of plasma-derived products, which are now mostly in the past. The promises of recombinant factor products are twofold. First, recombinant factor is a source of potentially unlimited FVIII, unrestricted by the intrinsic constraints of the plasma supply; the potential supply generated by cell lines is theoretically infinite. Second, recombinant products are conducive to bioengineering and manipulation towards improving FVIII levels and yield.

Increased Supply

The supply of FVIII products over the past 20 years of being in general use has steadily increased. The number of players has been fairly stable over the past 10 years but the supply has risen steadily. This suggests that manufacturing capacity and efficiency has increased. There have been many studies published on improvements in FVIII and manipulations on standard cell culture in relation to FVIII. A 2011 study on a lentiviral vector platform for the production of bioengineered recombinant FVIII showed that the technologies yielded production cell lines that biosynthesized the highest level of recombinant FVIII production reported to date. A study published in 2012 showed that bioengineering strategies aimed at different structural and biochemical attributes of FVIII have been successful in enhancing its expression levels and lead to synergistic improvements in FVIII secretion efficiency.

There are a number of new longer-acting products in clinical development based on different strategies to enhance coagulation factors via half-life extension (i.e., pegylated liposomes, random and site-specific pegylation, Fc fragment and albumin fusion proteins, and modification of amino acid sequence). Clinical studies are well underway and results thus far have shown a three- to fivefold increased half-life in the recombinant FIX and recombinant FVIIa products, and extended half-life in the recombinant FVIII products by 1.5 to 1.8 times. However, studies have described individual variations in the pharmacokinetics of coagulation factors. The International Prophylaxis Study Group (IPSG) Pharmacokinetics Expert Working Group has highlighted the importance of knowing individual patient half-life with the longer-acting products and cautioned that it is unlikely that once-weekly infusions will be suitable for all patients.

Prophylaxis Cost-Effectiveness

Prophylaxis has been established as the treatment of choice for children with hemophilia. Studies have shown that its continuation in the adult years decreases morbidity throughout life, but there is debate surrounding the cost-effectiveness of prophylaxis for adults. Prof. Farrugia has initiated a pharmacoeconomic study of the cost-effectiveness of prophylaxis vs. on-demand treatment for severe hemophilia A. With input from industry representatives, treaters and patients, the investigators assembled extensive data from international best evidence on the effectiveness of prophylaxis and developed a cost-utility model for lifelong prophylaxis vs. on-demand treatment. The model was

applied to three national health system contexts: the United Kingdom, United States, and Sweden (which has daily dosing for prophylaxis). In all three countries, prophylaxis was found to be superior to on demand therapy in terms of both cost and effectiveness. With the standard regimen of once every two or three days, the incremental cost-effectiveness ratio was within the range of what is acceptable for the payer agencies. Therefore, in terms of the conventional norms of healthcare reimbursements in these developed countries, hemophilia care based on lifetime prophylaxis is cost-effective.

Pricing

In terms of pricing, a 2002 analysis of the average unit price of recombinant FVIII in the U.S. from 1993 to 2000 showed that the price had declined from the initial price. The cost today has not kept up with inflation rates; if the price of recombinant FVIII had remained constant, the price today would be $1.45 per IU. There has been a slow but steady decline in price, primarily because of increased uptake in the bleeding disorders population.

Prof. Farrugia's pharmacoeconomic study found that the U.K. had the most favourable outcome in terms of cost per quality adjusted life year; the price of FVIII in the U.K., which uses a tendering process for the procurement of factor concentrates, is less than half the price elsewhere in the world. An article by Charles Hay published this year in *Haemophilia* on purchasing factor concentrates in the 21st century through competitive tenders provides interesting insight. Another study of plasma-derived FVIII and FIX prices in Brazil from 1997 to 2003 showed that after six years at a steady price, there was a notable drop in price in 2003, when purchasing processes were introduced for the acquisition of factor concentrates.

The economic concept of elasticity refers to how changing one economic variable affects others. The elasticity of demand basically relates to the quantity available on the market due to change in price. In most instances, treatment products of an essential nature such as factor concentrates are seen to be fairly elastic, in the sense that no matter how much prices are raised or lowered, there will be the same amount of supply because they are essential drugs. The more elasticity there is in the system, the more chance there is for an increase in price to lead to an increase in availability. There are studies available in the public domain about whether FVIII can be considered to be a special case of drug provision which is relatively elastic.

In conclusion, Prof. Farrugia reiterated that the treatment of hemophilia to optimal levels is cost-effective. While prices do remain high, there has been a steady decrease in price and the supply of all forms of FVIII has increased over the past years. As demand and consumption continue to rise, prices can be expected to drop further.

Discussion

Dr. Steven Pipe agreed that for patients with hemophilia, the more factor the better. However, the optimal treatment approach for patients with other factor deficiencies could differ in some ways. In his clinic, when there is a family history and diagnosis of FXIII deficiency, patients are given lifelong prophylaxis from birth to prevent joint bleeds and preserve joint function throughout their entire lives. The acceptable number of bleeds will be zero but their individual treatment regimens will not look like normal FXIII models because FXIII deficiency has a high degree of heterogeneity and variation in clinical manifestations.

Over the years, treaters have learned that there are differences in physiology, and a threshold by which it is possible to achieve a manageable treatment regimen that meets all the criteria for bleed prevention and joint preservation, but does not require zero bleeds or total normalcy, he continued. In hemophilia, particularly for the developing world, zero bleeds can be a lofty, unattainable goal because of cost or limited access to treatment. Is there a point that can accommodate the current and competing issues—a trough level that adequately meets the criteria but does not necessarily provide zero bleeds and total normalcy? Even within the framework of bleeding disorders, there are some discrepancies, where there is a continuum of replacement therapy that can provide the desired type of achievement and level of treatment success. The challenge will be to determine what the new regimens are like and the desired level of treatment; for example, through outcome-based studies on target levels and target regimens.

Prof. Farrugia agreed and said his definition of normalcy would be treatment whereby trough levels provide protection throughout life to the extent that people with hemophilia do not get joint bleeds, intracranial hemorrhages, etc. This could require something beyond the paradigm of 1% to 3% trough levels. For clinical studies, it is important to remember the precautionary principle to minimize risk to patients. While there might be a reasonable biological hypothesis that 3% is better than 1% trough level, at this point in the evolution of hemophilia treatment, it is no longer acceptable nor justifiable to randomize patients into a treatment regimen that is potentially insufficiently protective and can hypothetically cause harm, as the patients will have to contend with joint damage for the rest of their lives.

It is essential to acknowledge that FVIII half-life or delivery has to be improved because infusion every other day, or daily for some patients, is very difficult, and venous access is sometimes difficult in babies and young children, said Dr. Marilyn Manco-Johnson. There are physical and biochemical limitations that need to be overcome.

Dr. Marijke van den Berg said the concept of elasticity of demand is applicable to hemophilia treatment products. There is such great demand for factor products globally and manufacturers can produce greater volumes; the need and capacity exists. Cost is an issue and can also be a driver to have more products for more patients.

The Rise of the Patient Voice: Patient Perspectives on Clinical and Economic Aspects of Novel Treatment Products

MARK W. SKINNER, PAST-PRESIDENT, WORLD FEDERATION OF HEMOPHILIA (2004-2012)

The concepts of patient-centred care, shared decision-making, patient-based outcomes, and direct patient voice have become prominent in medical literature and part of the regulatory and healthcare funding discourse, said Mark Skinner. Patient care increasingly involves shared decision-making. The clinician and patient discuss the possible treatment options and outcomes in depth and the patient's goals related to treatment; then together, taking into account the clinical information, best scientific evidence and patient's preferences, they form a specific treatment plan. The patient voice is growing in influence and importance in healthcare and regulatory settings.

Over the last couple of years, Mr. Skinner has participated in PharmaFutures, a multi-year global investor-led dialogue on the future of the pharmaceutical industry. PharmaFutures has identified the emergence of a new patient voice which will have a dramatic influence in future discussions on healthcare coverage and reimbursement, and even clinical development processes. It also identified several trends in the United States, Europe, and emerging countries such as rising patient engagement due to healthcare reforms, and structural changes to integrate and develop care around individual patient expectations and preferences.

Patient involvement in the pathway for drug development typically occurs through clinical trials or in the post-marketing phase. In this new era of patient-centred care, patients will increasingly be involved early in the translation process, in discussions on natural history, actual outcomes, and clinically relevant endpoints that actually matter to the patients.

The U.S. Food and Drug Administration has fully embraced the notion of patient-centred care. The July 2012 Reauthorization Bill for the FDA designated specific funding for a Patient-Focused Drug Development Initiative, which will involve public meetings on specific disease areas to obtain patient perspectives on their disease and available therapies for their condition. Hemophilia is among the 20 diseases selected for the first series of consultations. "The expectation is that the whole world of regulatory science is going to change dramatically in the coming years and will really be built around how therapies add value to patients, and whether the value and benefits described by manufacturers align with patient preferences and interests," Mr. Skinner said.

One of the core provisions of the U.S. Affordable Care Act is a new federal agency called the Patient-Centered Outcomes Research Institute (PCORI), to build research guided by patients, clinicians, and the broader healthcare community. PCORI approved more than $300 million dollars in research grants in 2012 and committed more than $400 million dollars towards research in 2013. The ultimate objective is to produce evidence-based information to help people make informed healthcare decisions, and improve healthcare delivery and outcomes. PCORI has created a rare disease advisory panel to explore how to conduct this type of research in the field of rare diseases. "There are great opportunities to begin to change the discussion and the paradigm as governments look at rare diseases like hemophilia and other rare bleeding disorders which may have some data or evidence constraints," he said.

There is an increasing body of evidence, not just within hemophilia but across the spectrum of healthcare, that patient engagement improves care. The Foundation for Informed Medical Decision-Making notes that when patients are fully informed of all the available treatment options, they make choices that are more aligned with their preferences and values, which leads to a higher quality of care. There is also evidence of increased cost-effectiveness when patient values are aligned with decisions

on their care. "What matters to patients may be very different from what matters to regulators, payers, government officials or clinicians, so we must fully embrace the opportunity that is now at hand to become integral partners in the research agenda very early in the regulatory process and through the reimbursement and access phases," Mr. Skinner said.

A key issue for the bleeding disorders community is the transition to novel long-acting factor products, which could be introduced to the U.S. market as soon as early 2014. Patients and healthcare providers will require education and training on the novel products. It will also be important to educate payers and governments about the novel products, which will not fit neatly into tender systems and drug formularies. Health authorities will want to compare the novel therapies to existing treatment costs; it will be imperative for the bleeding disorders community to demonstrate the value of the new drugs in terms of the long-term patient outcomes. Regarding access and affordability, Mr. Skinner asserted that no patient should ever have to apologize for the cost of their care: "We need to demonstrate and identify what is appropriate and what is needed, then figure out how to work together to make it affordable and achievable."

Another important issue for the hemophilia community is defining trough levels for optimum care. Key questions include: What is the goal? To improve from severe hemophilia factor levels (0-1%) to moderate (1-5%), mild (5-50%), or normal (50-150%)? Better bleed protection? A reduced treatment burden? Reduced overall cost of care? "My shorthand definition of normal is having a life like someone who doesn't have hemophilia," Mr. Skinner said. "Currently with work, career, family, social life, sports and activities, functional mobility and other issues, I think most patients would say that their lives are not the same as people who do not have hemophilia." While 1% has long been accepted as the standard of care, it is time to re-evaluate whether it is the correct and sufficient target, and perhaps think about something better. "We know that normal is something different, 1% is just not normal," Mr. Skinner said. Normal would mean that even with longer intervals between infusions, a young child with hemophilia would be maintained at a therapeutic level that would allow him to engage in activities and play sports such as soccer just like his friends, he said. "People with hemophilia have a right to try to be normal and to have our condition cured, or at least normalized, so that we can live and fulfill the same opportunities as every other individual in society. Governments may have to rationalize, but at a minimum they should recognize that we have that right to be normal, to aspire to the complete absence of joint bleeds, and not accept anything less if the data tells us that a certain trough level is what we need to reach normalcy."

Mr. Skinner has initiated a multinational study on the views of patients with moderate and severe hemophilia with regards to the novel FVIII and FIX agents to be introduced in the next few years. The study is gathering information on patient values and preferences, and baseline information on their treatment goals, expectations and needs to help them live normal lives. There are currently three countries involved: Canada, Ireland, and the United States, in different phases of the study. Patients were surveyed and asked the following question: "What would you be looking for in your new treatments? Are you looking for reduced burden and reduced treatment frequency, or are you looking for better protection?" Among Canadian patients, the overall results were 57% and 43% respectively. It is important not to assume that reduced burden is the only goal, Mr. Skinner said. Currently, most of the debate has centred on prophylaxis vs. on-demand therapy, and treatment frequency. It is time to start the conversation with patients about trough levels with better protection and what a change in treatment paradigm can actually mean for them, he said. The goal is to publish the findings before the 2014 WFH World Congress, which should coincide with about the time the first novel products enter the market in the U.S., Canada, and possibly Australia.

Currently, the goal of prophylaxis in a patient with severe hemophilia is to maintain a trough level of greater than 1%. This trough level in essence converts severe hemophilia to moderate hemophilia, and therefore provides limited success as a cure. In gene therapy research for hemophilia, achieving a 1% trough level would not be considered a successful long-term cure, Mr. Skinner noted. A recent Dutch study showed that absence of joint bleeding might only be reached when approaching about 15% trough levels. While treatment at such high levels are currently out of reach given the high cost of factor concentrates, the finding that 15% actually achieves a functional cure gives patients and doctors a specific level to aspire to in order to have complete absence of joint bleeds.

The new long-acting factor products coming to market provide an opportunity to rethink target trough levels and at least move towards 15% to improve outcomes and further normalize the lives of people with hemophilia. "Economics should not limit our treatment goals. It may be a pragmatic reality to contend with but from a scientific standpoint we need to establish what is needed, correct and appropriate, and what patients value and seek in treatment, and then set about figuring out how to pay for it," Mr. Skinner said. At the same time, patients will have different preferences and circumstances, therefore, personalized treatment will be the cornerstone of hemophilia care in the coming years.

Mr. Skinner proposed that manufacturers consider a new business model with the new drugs coming to market, based on higher volumes and lower margins. "If we really try to address the unmet need in the world, there should be the opportunity for a win-win situation all the way around," he said. "While it's reasonable to expect that the optimization and innovation of the new treatment products will be translated in the final price, I'm not ready to concede that the new products will necessarily be more expensive. The change in treatment paradigm will have costs, but don't assume that the cost per unit or the cost per year for a patient necessarily has to be more expensive. There is great potential for competition and we could see downward pressure. The simple laws of supply and demand suggest that if we increase the supply, moving to a volume business, demand will increase, and prices will become more competitive," he concluded.

Discussion

Referring to Mark Skinner's multinational study on patient perspectives on novel hemophilia drugs, David Page said that at a recent Canadian Hemophilia Society camp retreat for fathers and sons in Ontario, Canada, they discussed the new extended half-life products and many gained a deeper understanding of the benefits and possibilities that better protection will bring to their lives. Some boys said daily prophylaxis would be worthwhile in exchange for 10% factor levels every day.

Dr. Marijke van den Berg said it is important to acknowledge how many years it has taken to start prophylaxis in the United States, while Europe has collected a lot of evidence. Randomized control trials are not necessary; studies would be a matter of elevating factor dose level in moderate amounts to raise trough levels and following patients through observational studies and natural experiments. Reducing treatment burden is important; in some cases, it makes sense to switch to daily infusions and have smaller vials.

Dr. Marilyn Manco-Johnson said there are different needs within the community and different populations that need to have different discussions. It is important to discuss the psychological aspects of on-demand treatment compared to prophylaxis. Shifting from on-demand to a proactive, preventative approach empowers patients because they are able to understand, predict, and control their bleeding.

Mr. Skinner said the bleeding disorders community is at a point in time with a critical opportunity to reassess the optimum level of treatment to achieve the absence of bleeds and define a new normal for people with hemophilia. The new products are coming to market and the revolution in treatment will begin. Some patients may simply want reduced frequency of infusions; however, the multinational study's preliminary data suggests that there are a significant number of patients who want something more. The new therapies offer the opportunity to personalize care. It is important for all patients to understand what the different products offer and the benefits or trade-offs in choosing one over another, so that they can make informed decisions about what is right for them.

There are many different views based on generation and individual experience, said Brian O'Mahony. For someone who has had no access to treatment, on-demand factor therapy is great; for someone who grew up with on-demand therapy, prophylaxis is great; someone who has grown up with prophylaxis will want something better. The concept and goal of a 15% trough level is desirable but it is important to be pragmatic and try to determine what is currently achievable and what can be achieved over the coming years through steady and incremental improvement.

It is important to remember the need to provide individual choice, based on different factors related to the patient's treatment, condition, and wishes. Some may have venous access problems and want less frequent infusions; others will want higher trough levels and greater protection from bleeds to engage in certain sports, activities or occupations. Crucially, this year the European Directorate for the Quality of Medicines accepted a recommendation that has been made over the years that prophylaxis for adults should be available on an individual basis, based on discussion and decision-making between the clinician and the patient.

What benefit of longer-acting products has the greatest appeal to you?

Similar trough levels but lower frequency of infusions	39%
Similar frequency of infusions but higher trough levels	61%

Based on your knowledge of patients in your country, what percentage do you think would prefer higher trough levels over reduced frequency of infusions?

0-25%	7%
25-50%	50%
50-75%	16%
75-100%	7%
I don't know	20%

Clinicians: If affordable, what percentage of your patients do you think would benefit from higher trough levels?

0-25%	4%
25-50%	17%
50-75%	4%
75-100%	71%
I don't know	4%

Patients: What would be the effect of lower frequency of infusions on adherence to prophylaxis?

It would increase adherence	53%
It would decrease adherence	13%
It would make no difference	23%
I don't know	11%

DAY 2: SEPTEMBER 27, 2013

SESSION 3: PRODUCT CHOICE – WHAT DOES IT MEAN?

CHAIR: MARK W. SKINNER, PAST PRESIDENT, WORLD FEDERATION OF HEMOPHILIA (2004-2012)

There are rapid developments in the world of bleeding disorders treatment and coming changes with a number of new products about to enter the market, said Mark Skinner. A host of novel recombinant products will join the many plasma-derived and recombinant products that currently exist. Still, there will be an ongoing need for plasma-derived products in developing countries where treatment supplies are often in short supply or non-existent. To set the framework for a plenary discussion, four panelists shared different perspectives based on their experiences in the regulatory, industry, clinical, and patient advocacy fields.

Who should determine which products are available to treat patients within a country?

Clinician	10%
Patient	1%
Regulator	13%
Payer (Health Ministry/Insurer)	4%
Combination of Clinician, Payer, Regulator	25%
All of the above	45%

Who should make the final choice of product used to treat an individual patient?

Clinician	17%
Patient	14%
Regulator	0%
Payer (Health Ministry/Insurer)	0%
Combination of Clinician and Patient	66%
All of the above	3%

How much clinical freedom is needed?

All recombinant products should be available	4%
All plasma-derived products should be available	0%
All recombinants and plasma-derived should be available	57%
Only 1 or 2 from each product class need to be available	28%
Uncertain	10%

Are recombinant treatment products interchangeable / therapeutically equivalent?

Yes	35%
No	43%
Uncertain	22%

Are plasma-derived treatment products interchangeable / therapeutically equivalent?

Yes	34%
No	56%
Uncertain	9%

Panel Discussion: What Do We Mean By "Product Choice"?

Albert Farrugia, Vice President Global Access, Plasma Proteins and Therapeutics Association

The question of product choice is very different in different parts of the world, said Albert Farrugia. This was evident from the first WFH Global Forum in 2000, in the debate between Ashok Verma of Hemophilia Federation India and Mark Skinner of the U.S. National Hemophilia Foundation (NHF) on the question of risk acceptability. Mark Skinner at the time underlined the NHF's zero tolerance position on even theoretical risk in blood products, while Ashok Verma pressed for access and supply in the developing world and expressed a total willingness to accept factor products that were withdrawn from some countries and being destroyed due to theoretical risks such as variant Creutzfeldt-Jakob disease. "The sober reality is that choice is not an issue in most of the world," he said. "Most of the world's patients would be very happy and willing to get access to any product, irrespective of what it is. Therefore, the first issue is how to increase access globally and the ways in which this can be done."

The issue of product choice resonates with the debate on whether the future lies in plasma-derived or recombinant products, and the question of whether blood services in developing countries will develop in the same way they developed in industrialized countries in the 1960s—primarily driven by the need for FVIII. It is possible that a recombinant product will become very widely available and accessible in the developed world before a paradigm is devised for delivering plasma-derived products to the developing world. Blood transfusion services would first need to develop good manufacturing practices for blood transfusion in order to generate plasma. However, besides lacking infrastructure and resources, the basic mission of blood transfusion services in the developing world is to provide blood components for routine and emergency transfusions, not plasma for the manufacture of products for bleeding disorders.

On the matter of clinical freedom, he said: "Clinicians must have the freedom to get the product that is most appropriate for the patient at that time—they are very expert in individual patients and how to tailor therapy. It should not shaped by the excessive implementation of product choice strategies by health authorities and governments as a route to minimizing price."

Some countries with mechanisms such as national tenders and procurement schemes have managed to produce a product choice landscape with a multiplicity of players. One predominant player is chosen, with the result that prices can be moderated downwards. However, it is dangerous to let a single player or monopoly dominate the market. "It is not possible to regulate or to ensure supply for an essential class of lifesaving drugs," said Prof. Farrugia, formerly Australia's blood regulator. The multiplicity of players and products entering the market will be good for the global bleeding disorders community, and hopefully there will be rising demand and supply.

Brian O'Mahony, Chair of WFH Treatment Product Safety, Supply and Access Committee, and President of the European Haemophilia Consortium

While Europe is a wealthy region of the world, there are major differences and vast disparities in the availability of hemophilia treatment and care across the continent. "The reality is that the cost of products, budget constraints, and lack of willingness of governments to prioritize hemophilia care all limit the availability of treatment," Brian O'Mahony said. "In the past five years, with the economic downturn, governments have been looking at health technology assessments, cost-utility analysis, cost-effectiveness, and cost-benefit analysis, and this is not going away."

A 2012 European Haemophilia Consortium (EHC) survey of 35 countries found a wide range in FVIII usage per capita, from 0.2 IU per capita in Armenia to 8.56 IU per capita in Sweden, and that consumption was not fully dependent on the GDP. National tenders were used for the purchase of factor concentrates in 17 countries, including in a number of countries which had significantly improved access and supply since the previous survey in 2009. Ireland has had a national tender system in place since 2003, with the full involvement of the patient organization and physicians. Factor availability and usage has increased steadily over the years despite the economic downturn and a 17% decrease in the health budget since 2009; from 1.3 IU per capita in 1996 and 3.5 IU per capita in 2003 (prior to implementation of a national tender system), to 8.12 IU per capita in 2012.

The level of knowledge about hemophilia treatment products and clinical developments varies widely among physicians and patients alike; some have extensive scientific understanding while many have limited or cursory knowledge. The EHC has given training courses on advocacy and national tenders for a small number of hemophilia society leaders.

Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form and route of administration, and are identical in strength or concentration. In the audience poll on whether recombinant products are interchangeable/therapeutically equivalent, 35% voted yes and 43% voted no; on plasma-derived products, 34% voted yes and 56% voted no. Mr. O'Mahony said the issue of therapeutic equivalence in hemophilia, and its ready acceptance by physicians and hemophilia societies, is a major concern. "There are small differences between the recombinant products and differences between the plasma-derived products that need to be analysed and considered. They should never be excluded from the decision mechanism because then cost becomes the only criteria," he said.

With acceptance of therapeutic equivalence, the risk and actual consequences are that tenders can take place without input from physicians or hemophilia society leaders, with government officials alone making the decisions based on cost. "There might be no bad products at the moment, but we should learn from history that as physicians and as patient organizations, we need to always take a view on these products," Mr. O'Mahony said. Under European Union law, selection of treatment products can made be on the basis of price or the most economically advantageous tender. "Cost is always a high factor in the decision but it is a major mistake to not look at safety, efficacy, quality, availability of supply, scientific support, and the other factors," he said. He warned that as countries tighten their health budgets, some health authorities are starting to interfere in clinical decision-making, questioning prophylaxis regimens and proposing less therapy. "If physicians and hemophilia society leaders do not insist on having a role in the selection of products, if you abrogate your responsibility, if you leave that decision to officials with no real knowledge of the products, then you're going to have major problems," he said.

Vigilance, knowledge, and full involvement of physicians and patient leaders in the selection process are critical. In some countries, the society and physicians are fully involved in every step of the tender process and participate on advisory committees to advise the Ministry of Health on product criteria and choices. "Price must and will always be a factor of consideration, but it should not be the sole consideration," Mr. O'Mahony said.

National, regional or multi-country tenders are effective as long as the key physicians and patient organizations are involved. In the U.K., the tender has had a positive impact on price, in effect setting the price spans, and all of the products are available. Ireland's tender achieved a similar outcome in terms of reduction of cost but not all of the products are available. Having the choice of all products available is not absolutely necessary, particularly in smaller countries with lower factor usage.

Limited choice is a good solution as long as the choices are made by the right people, he said. Safety, efficacy, and quality are always crucial and of high importance in selection criteria for products. It is essential to have a procedure to deal with exceptional cases as there will always be individuals who are not suited to the chosen product.

The key doctors and hemophilia societies must be involved formally in tenders, ideally training together with health officials. The WFH has held training courses involving health ministry representatives, procurement officials, physicians, and the hemophilia societies in Brazil, Peru, Lebanon, and Ireland.

Nigel Key, Director, UNC Hemophilia and Thrombosis Center, Chapel Hill, North Carolina, USA; Vice President Programs, World Federation of Hemophilia

The U.S. healthcare system is not a single payer system—each state has its own Medicaid system and ability to choose what products are available and, furthermore, the products covered by health insurance companies belonging to the Blue Cross Blue Shield Association differ state by state, said Dr. Nigel Key.

At the UNC Hemophilia and Thrombosis Center, treaters and patients do not have product choice as inpatients but do as outpatients. A patient who chooses a particular product as an outpatient could as an inpatient face a different set of negotiations and contracts with third-party payers. Physicians have input on what products to allow for use but the hospital pharmacy does not stock all of the products.

Driving competition is very important but it does not necessarily drive down the price. National tenders, however, can effectively drive down price. Middleman mark-ups in the U.S. health system affect price; it is not always the manufacturer price but the price charged to the third-party payer that can be tremendously high. Dr. Key strongly advocated in favour of patients and physicians working together towards access to product choice: "We have to have choice. The constraints being put upon us by third-party payers are a bit of a myth and not the reality, in a country where all products are available."

Dr. Margareth Ozelo, Director, International Hemophilia Training Centre, University of Campinas, São Paolo, Brazil

The availability of hemophilia treatment in Brazil has progressed through different steps as it has evolved from a developing country to an emerging one, said Dr. Margareth Ozelo. Two decades ago, there was a lack of products available to provide adequate care. At that time, plasma-derived products were the only option available. "The first basic choice is to simply have at least enough product to treat patients on demand," she said.

In their first political foray, an advisory board of hematologists, hemophilia society representatives, and other experts was formed to make recommendations to the Ministry of Health on increasing product access and supply and the purchase of factor concentrates at feasible prices. There was outreach to identify and diagnose people with hemophilia and a patient registry was established. "Diagnosis and patient registries are key and very important when sitting at the table with governments to discuss how much product is needed and how much it will cost," Dr. Ozelo said.

Availability of treatment products gradually increased step by step; first, they gained enough supply to provide the hemophilia population with on-demand treatment, then one-dose home treatment, followed by full-dose home treatment, and finally primary prophylaxis.

As for product choice, Dr. Ozelo said she never had the option to choose a particular product for her patients. The centre usually had different brands of plasma-derived products and physicians used whatever product was available at any given time. "Using a different product each time may not be ideal but there weren't critical consequences," she said. "What was important was that we needed to have enough product and for the product to be safe."

In 2003, Brazil introduced a tender system for the purchase of treatment products. Hematologists and hemophilia society representatives participate in tenders by informing the Ministry of Health about the specific products and quantities desired and the parameters for safe, quality products; they do not participate in the actual tendering process with manufacturers. Products are selected on the basis of lowest price and parameters set out by clinical experts and patient leaders.

Over the past decade, the government has gradually increased the budget for hemophilia care, the parameters have expanded, and patients now have access to recombinant products for bleeding disorders. "It was a long, step-by-step process," she said.

Discussion

Tenders and Procurement

Matt Gregory of the U.K. Haemophilia Society said it is important to have as many companies tendering as possible and to have the maximum patient choice possible. Understandably, smaller tenders for lower quantities of product would attract fewer companies to tender.

Brian O'Mahony said when a big tender is involved, such as in Canada, Australia, or the U.K., all the companies generally put forward tenders. With smaller tenders it can be difficult to get companies to tender because of the small quantity involved; this can result in limited choice and a limited number of products licensed in a country. In his view, limited choice is acceptable if the tender process involves informed individuals, particularly clinicians and patient representatives. In terms of the price of product, not just the price charged by the companies, Ireland has been able to increase FVIII usage from 3.5 to 8.2 IU per capita at a time when its economy was plummeting in terms of GDP. Ireland now has more competitive tenders, better prices per unit, and no handling fees. Some of the savings achieved from the elimination of handling fees, which used to comprise about 20% of the cost, are channelled back to hemophilia treatment centres. If there are any savings in the hemophilia budget, funds should be put towards comprehensive care, facilities, resources, and additional medical and nursing staff, he emphasized.

Dr. Alok Srivastava said that tender processes should ideally involve well-informed and conflict-free patient organization leaders and medical experts within the government system. It is important to collect data on the different existing products and maintain ongoing surveillance of their safety and efficacy post-marketing authorization, in order to be able to make informed recommendations in future tenders.

Dr. Marijke van den Berg agreed: "Physicians and patient representatives should be involved in tenders and involved in making the decisions, but the community cannot go further advocating for product choice without collecting the supporting data on the differences between the products."

Patient organizations and clinicians must work together to collect data on treatment products and outcomes, otherwise choices and decisions will be made by payers on the basis insufficient information, said Mark Skinner.

Interchangeability and Supply

David Page said the key issue is interchangeability—whether the products are interchangeable or not. There isn't much data showing that there is an increased risk with one product compared to another, nor much greater inconvenience with one or another. However, a tender that selects just one supplier and product based on lowest price would be a dangerous choice as supply issues could arise and it may be difficult to get the same good price subsequently or elsewhere. Tenders have to balance cost with security, supply, and issues related to competition. There are also issues where some individuals have different adverse reactions to different products. These patients need access to all the products on an individual named patient or special access basis—this needs to be protected.

Mr. Skinner noted that in the audience poll on interchangeability of recombinant products, 35% voted yes, 43% voted no, and 22% were uncertain. Opinion was more conclusive on plasma-derived products; 34% voted yes, 56% voted no, and 9% were uncertain. The issue with interchangeability is whether a physician or patient who chooses a specific drug for treatment would be compelled to substitute it with a less expensive drug after a tender or selection process through which a group of drugs has been vetted and deemed therapeutically equivalent. This is the scenario currently in the United States; if the patient continues to want a specific drug, they may be asked to pay the cost differential because less expensive therapeutically equivalent therapies are available. Medicines for hemophilia have typically been excluded from the formulary tiers based on pricing. Is product choice a necessity or a luxury?

Mr. O'Mahony said this question arises frequently in discussions on tenders in hemophilia, with the concern being whether a tender could result in a change of product and whether product switching might bring a higher risk of inhibitors. There have been studies published in Canada, the U.K., and Ireland on large numbers of patients who switched products, which showed no increased risk of inhibitors. As Dr. Nigel Key noted, a patient may be treated with a different product than usual in an emergency situation. In some developing countries, the treatment depends on whatever product is available at a given time. While very frequent product switching is not desirable, switching every few years is acceptable if it involves a safe, effective product that has undergone a rigorous selection process.

Dr. Margareth Ozelo said for the past 15 years in Brazil, the plasma-derived products available changed all the time. The important requirement was to have a supply of safe products to be able to treat patients at the clinic. Physicians advise the Ministry of Health of their minimum requirements in terms of safety, efficacy and quantity, and are comfortable with the products made available. Real data from these years show that patients who received two different products in a single month had no adverse effects. This may not be ideal but when no other product is available, the only alternative would be to not treat the patient. Potential issues related to product switching highlight the importance of surveillance systems to be able to detect adverse events such as inhibitors and assess whether previously treated patients are particularly susceptible, said Dr. Nigel Key.

Dr. Steven Pipe cautioned that studies and data on the interchangeability of products should not be used to limit the availability of product choices. For example, should a study show that a specific product has the lowest inhibitor risk, regulators could potentially declare that product as the only one to be used by patients. It is important to maintain a competitive landscape with many product choices because at different levels, somebody will have a preference for a specific type of product

based on various factors such as ease of administration, vial size, brand, etc. These market forces drive competition and ensure that other companies want to be part of the landscape. There is still room for additional products and niches.

The United States is clearly the dominant growth market in the world for biologics, if not hemophilia, said Mr. Skinner. The European market is static, if not shrinking, at least in terms of return for manufacturers, because of the downward pressure on costs. The emerging countries—Brazil, Russia, India and China—are the next big growth market and will help shape this debate going forward.

Safety and Surveillance

Dr. Marilyn Manco-Johnson said the hemophilia treatment centre at The Children's Hospital in Denver, Colorado, has just undergone three years of intensive revamping and now has a safety and efficacy surveillance system that collects data such as number of bleeds, infusion frequency, immunizations, major bleeds, surgeries, inhibitor development, and the specific products used. There are currently about 7,000 people with severe hemophilia in the registry. In the next year or two, there should be sufficient data collected to discern whether or not the new factor products are more immunogenic than the traditional products, and whether or not there are differences between products in terms of viral safety, bleeding protection, and inhibitor risk. It is important to have a range of product choices and allow for individual patient preferences. Post-marketing surveillance is essential with new products or product switching. It would be beneficial to have a more holistic, structured and comparable approach for product surveillance.

Dr. Michael Makris said in the U.K., the amount paid for factor concentrate is now about to drop by 55-60% relative to the price six years ago. However, none of the savings have been channelled back to hemophilia care because of an oversight and failure to negotiate with the government that if the overall price of treatment decreases, the funds saved would be used to improve services. The challenge now will be securing funding if the price of treatment rises.

Dr. Johannes Blümel of the Paul-Ehrlich-Institut in Germany said he and his co-investigators presented research on 10 years of safety and effectiveness with the FVIII concentrate product Advate® at a recent meeting of the International Society on Thrombosis and Haemostasis and are in the final stages of submitting the manuscript for publication. The study encompasses 87,000 patient-years and close to 14 billion IUs delivered. The study differs from others in that it focuses on efficacy in a highly controlled clinical setting, which is different from real world use. It is important to look into the variances in different countries and variances reported by different sources. Dr. Blümel urged other companies to also disclose the information in their pharmacovigilance databases.

Pam Foulds of Biogen Idec said the company works closely with physicians and patient organizations and is looking for ways to combine the available data on their products to fit with the new regulatory requirements.

David Page noted that there are big differences in recovery and efficacy among the FIX products currently available on the market, therefore, product choice is certainly necessary on an individual basis as new products come along. While the dose and infusion frequency of the current products can be adjusted to reach any desired trough level, as can be done with the new long-acting products, venous access is an issue, particularly in young children, so there may be people who cannot reach higher trough levels with that frequency in an easy way.

Who should determine which products are available to treat patients within a country?

Clinician	7%
Patient	2%
Regulator	2%
Payer (Health Ministry/Insurer)	2%
Combination of Clinician, Payer, Regulator	33%
All of the above	55%

Who should make the final choice of product used to treat an individual patient?

Clinician	15%
Patient	7%
Regulator	0%
Payer (Health Ministry/Insurer)	3%
Combination of Clinician and Patient	70%
All of the above	4%

How much clinical freedom is needed?

All recombinant products should be available	5%
All plasma-derived products should be available	0%
All recombinants and plasma-derived should be available	61%
Only 1 or 2 from each product class need to be available	29%
Uncertain	6%

Are recombinant treatment products interchangeable / therapeutically equivalent?

Yes	28%
No	58%
Uncertain	14%

Are plasma-derived treatment products interchangeable / therapeutically equivalent?

Yes	28%
No	58%
Uncertain	14%

SESSION 4: THE IMPACT OF REGULATORY FACTORS ON PRODUCT ACCESS

CHAIR: BRIAN O'MAHONY, CHAIR, WFH TREATMENT PRODUCT SAFETY, SUPPLY AND ACCESS COMMITTEE

Development of new medications for rare bleeding disorders is costly because of the limited market for these drugs. Over the past 20 years, regulatory authorities around the world have introduced orphan drug legislation to encourage research and development of treatment for rare diseases, with incentives such as market exclusivity, tax credits, and research support. While orphan drug legislation helps stimulate research and development of new medications for bleeding disorders, there are some practical challenges as well as concerns that market exclusivity limits competition and can have negative impacts on price and access to products. Similarly, regulatory guidelines on biosimilarity and interchangeability present both potential benefits and challenges. This session focused on the impacts of regulatory policies on drug research, clinical development, and access to bleeding disorder treatment products around the world, and implications for clinical practice.

Orphan designation, market exclusivity, biosimilarity and interchangeability: Is there a contradiction in regulatory policy and clinical practice?

Yes	57%
No	4%
Maybe	14%
Don't know	25%

Orphan Designation and Market Exclusivity

FLORA PEYVANDI, MD, PHD, DIRECTOR, DEPARTMENT OF INTERNAL MEDICINE, ANGELO BIANCHI BONOMI HEMOPHILIA AND THROMBOSIS CENTER, UNIVERSITY OF MILAN, ITALY

Dr. Flora Peyvandi gave an overview of orphan designation and market exclusivity and challenges related to the new long-acting factor products now in clinical development.

The rare disorders are a group of heterogeneous diseases with one thing in common—they are rare, low-prevalence diseases. But the numbers and the prevalence for each disorder are quite different. There are an estimated 6,000 to 8,000 rare disorders, 80% of which are genetic in origin and affect children at a very early age. In the United States, a disease is considered a rare disorder when it affects less than 200,000 inhabitants of the general population. In European countries, a rare disorder is defined as a life-threatening or chronically debilitating disease that affects fewer than 5 per 10,000 inhabitants.

The cost of developing and marketing a medicinal product for the diagnosis, treatment or prevention of a rare disease is not recoverable through the expected sales of the product under normal market conditions, as for the common disorders. Therefore, in several jurisdictions, specific legislation has been introduced to stimulate the development of drugs for rare diseases, called orphan drugs. Europe introduced orphan drug regulation in 2000, relatively late compared to the other areas of the world. The U.S. Orphan Drug Act was introduced in 1983, Japan's Orphan Drug Regulation in 1993, and Australia's Orphan Drug Policy in 1998.

The European Medicines Agency (EMA), through its Committee for Orphan Medicinal Products, is responsible for reviewing designation applications from persons or companies who intend to develop medicines for rare diseases, known as orphan medicines. In its first decade, 2000-2010, the European orphan drug regulation has led to the designation of 684 orphan drugs; 63 orphan drugs have received marketing approval, 12% in the field of hematological disorders.

The EU orphan drug regulation is highly appreciated for its role in creating a favourable environment for orphan drug development. The development of orphan drugs is stimulated through a number of regulatory and economic incentives. There are mainly three types of incentive measures: market exclusivity of the orphan drug, during which no other drug will be approved for the disease in question; tax credits and research support; and the simplification of the drug authorization procedure and related advantages.

The time period of market exclusivity granted varies geographically; 5 years in Australia, 7 years in the U.S., 10 years in Japan, and 10 years in the European Community for adult drugs and 12 years for pediatric drugs. During this period, orphan drugs benefit from market exclusivity and similar directly competitive products cannot normally be placed on the market. However, the European legislation also includes three types of derogations which allow for all or part of the legal measure to be applied differently or not at all: consent of the original marketing authorization holder; inability of the original marketing authorization holder to supply sufficient quantities; or the second medicinal product is safer, more effective, or otherwise clinically superior.

To qualify for orphan designation, three conditions must be fulfilled:

- the drug must be intended for the treatment, prevention, or diagnosis of a rare disease which is life-threatening or chronically debilitating;
- the prevalence of the disease should be not more than 5 in 10,000 in Europe (200,000 in the U.S.) or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development;
- no satisfactory method for diagnosis, prevention, or treatment of the condition can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

Hemophilia is a rare inherited bleeding disorder. Hemophilia A affects about 1 in 5,000 males while hemophilia B affects 1 in 30,000 males. The disorder is associated with bleeding episodes affecting soft tissue, joints and muscles, and repeated hemorrhages resulting in chronic arthropathy with loss of joint movement, fixed flexion contracture, and severe muscle wasting. Without proper treatment, it is life-threatening and chronically debilitating. Thus hemophilia meets the conditions for orphan disease designation, and the newer hemophilia drugs could qualify as orphan drugs and benefit from economic incentives including market exclusivity for some years. However, could the market exclusivity potentially create a monopoly, rather than market competition that ensures the widest possible access and most affordable prices? A particular concern in Europe is the regulatory requirement to conduct pediatric clinical studies, which means that European market authorization for the new products will likely occur two to three years after they become available in the U.S., and after prices are already established.

The key concepts for orphan drug designation and market exclusivity are significant benefit—a sponsor must demonstrate that their drug is better than what has been reported before—and the definition of similar product when a company has to demonstrate that their drug is not similar to what has been reported previously. If satisfactory treatments already exist in the field of hemophilia,

how should sponsors establish that their product would be a significant benefit and better than what has been reported until now? Many hemophilia products are available, from plasma-derived products to four generations of recombinant products. Yet there are still some challenges that could be resolved with better products in the future. The prophylactic regimen requires infusions two to three times weekly. Immunogenicity is a serious problem. The cost of products is not manageable in most countries and as a result about 70% of people with hemophilia worldwide do not receive adequate treatment. The challenges for the new generation of hemophilia products will be to provide greater safety, reduced immunogenicity, enhanced efficacy, prolonged half-life, lower cost, improved delivery, and increased availability.

Different companies are working on the extension of factor half-life via pegylation, Fc fusion, and albumin fusion. There are very interesting therapeutic strategies being pursued for patients with hemophilia including those with inhibitors. If these products are successful, it will bring dramatic changes to treatment because patients could be treated once every two weeks or once a month. Clinical trials for recombinant Fc fusion FVIII and recombinant Fc fusion FIX have been completed, presented to FDA and granted marketing approval, but cannot yet be presented to the EMA pending completion of pediatric studies. The key issues are how to judge whether one drug is better than another, and whether there is enough information and data to do so. Clinical studies show that long-acting FIX will bring a three- to fivefold increase in half-life and require fewer infusions, while long-acting FVIII will increase half-life by 1.5 to 1.8 times. The hemophilia community will welcome the new products; however, it is not actually clear which of these drugs will result in the best clinical outcomes in the long term. At this stage, one drug has market approval and when it becomes the first new drug on the market, there will be no competition from other companies.

There are also challenges in terms of how the product similarities and differences are described. It is very important for regulators to truly understand the principal molecular structures of the products and the mechanisms of action, but this is not always the case. In fact, the products all have different molecular structures; there are different recombinant proteins, cells, pegylation molecules, and fusion proteins being used. “They should be considered different products,” Dr. Peyvandi said. As to whether market exclusivity creates a monopoly and reduces competition, one study identified important marketing targets such as market size, turnover of the first orphan medicinal product, disease class, disease-specific scientific output, and age of onset. Better studies and better-designed studies are needed in the field of hemophilia, particularly with the arrival of the long-acting products.

In June 2013, the European Haemophilia Consortium communicated its position on orphan drugs to the EMA: “Orphan drug designation should not be used to hinder the development, licensing and marketing of other products for the same condition which have demonstrably different protein modification or enhancement.” The EU is allowed to approve a follow–on orphan medicinal product subsequent to the first orphan medicinal product, provided that significant benefit to those affected by the condition can be established. Significant benefit means a clinically relevant advantage or a major contribution to patient care, and is justified by demonstration of potentially greater efficacy, an improved safety profile, and/or more favourable pharmacokinetic properties than existing methods. This highlights the need for good data on the structure, efficacy, and adverse effects of each product.

Critical evaluation is needed on the missing follow-on orphan medicinal products to determine whether they are missing because of market exclusivity or due to matter of time or market size. Orphan drug designation and market exclusivity should be considered for those coagulation disorders with no available treatment products, such as factor V deficiency.

Market Exclusivity for Hemophilia Products: How To Consider The New Extended Half-Life Factors

JERRY POWELL, MD, PROFESSOR OF HEMATOLOGY AND ONCOLOGY, DIRECTOR OF THE HEMOSTASIS AND THROMBOSIS CENTER OF UNIVERSITY OF CALIFORNIA AT DAVIS, CALIFORNIA, USA

There has been tremendous progress in hemophilia over the past half century. In 1960, people with hemophilia had a life expectancy of about 20 years. The discovery of FVIII-rich cryoprecipitate in fresh frozen plasma in 1964, along with the development and licensing of factor concentrates in the late 1960s, dramatically improved hemophilia care and patient outcomes. In 2013, people with hemophilia on prophylaxis therapy essentially have almost normal life expectancy and almost normal quality of life. The main concerns are intracranial hemorrhage, spontaneous bleeding, and medical complications associated with central venous access devices (infection, sepsis, and thrombosis). "The major cause of morbidity and mortality in hemophilia remains spontaneous bleeding and clearly much more work needs to be done in the future," Dr. Jerry Powell said.

Current FVIII products display a half-life of 8-12 hours and require frequent infusions for prophylaxis. In a sense, it has taken several decades of evolving science and technologies for pharmaceutical companies to develop new factor concentrates with extended half-life, which will provide patients with prolonged hemostatic protection and require less frequent infusions. Several extended half-life products will soon be available on the market. "The key reasons for this progress in hemophilia are the advances in science, patients who demand progress, and the profit incentive which motivates pharmaceutical companies in the development and manufacture of life-saving medicines," he said.

The purpose of orphan drug designation is to grant special status to a product for the treatment of a rare disease. Market exclusivity for orphan drugs provides an incentive for scientists and pharmaceutical companies to invest in the research and development of treatments for rare diseases; for example, factor V deficiency, which affects about one in a million people. Should market exclusivity apply to the realm of hemophilia? Hemophilia is a rare disease; hemophilia A affects about 1 in 10,000 males, and hemophilia B affects about 1 in 25,000 males. However, the global market for FVIII concentrates in 2016 is projected to reach $11.4 billion in 2016. "The market is clearly sustaining a lot of interest and research—it is not an orphan drug situation and in no way does it justify a monopoly or market exclusivity," Dr. Powell said.

Patents for recombinant products introduced 20 years ago are now beginning to expire, yielding tremendous opportunities. The many new products for hemophilia in clinical development include: FVIIa and FX bypassing agents; FVIIa, FVIII, and FIX fusion Fc antibodies; rFVIII and rFIX albumin fusion proteins; pegylated FVIII; glyco-pegylated FIX-GP; TFPI inhibitors; anti-sense RNA for antithrombin; and human cell line factor VIII.

Moving forward, it is important to address several concerns: half-life considerations, adverse side effect profiles of the different extended half-life products, and inhibitor development. Frequency of dosing is determined by FVIII half-life, deemed to be 10 hours for currently available FVIII products, but individual variation ranges from 6 to 16 hours, according to one particular study. With the new extended half-life products, the question is: Can clinicians predict the half-life and benefit for each individual patient? According to results from pharmaceutical clinical studies, the new factor products, depending on the mechanism and on the individual patient, provides a 1.5 to 1.8 mean increase in half-life. Individual variations make an enormous difference in the total cost of factor products for a hemophilia treatment centre, insurer, company, or national health system. The variability is markedly

increased with the extended half-life products. Going forward, the variability could range from 7 to 32 hours, with tremendous implications for how those products will be used. "We need the flexibility to study the products after marketing—if a tender limits us to one product, we may not have the ability to answer those questions," Dr. Powell said.

With several products coming to market, which product will provide the maximum advantage for each patient? There will be variability in half-life extension from different mechanisms and for individual patients depending on their individual physiology, Dr. Powell noted. Other important questions include: Will the different mechanisms of action and molecular modifications produce different side effects? Which factor product will provide a lower inhibitor rate and in which hemophilia patients according to genotype/phenotype? "There are many clinical questions and market exclusivity could hinder patients and physicians from answering them," he cautioned. "Patients and doctors need to be allowed the choice and flexibility to see what product allows them to personally have the greatest benefit, and to make that decision independent of other considerations."

These are exciting times for hemophilia, with many products in development and the imminent arrival of extended half-life products and other options that influence the coagulation cascade. "Efforts by pharmaceutical manufacturers have been driven by the large market for FVIII and FIX concentrates and projections for the future—the profit incentive is critical for the future of hemophilia," Dr. Powell said. However, there are many unanswered questions about each product. There are also many different needs to be resolved for patients with hemophilia; each patient will have their own specific concerns. Market exclusivity could artificially interfere with addressing these questions with the flexibility and speed needed to continue to have progress in hemophilia, he said.

In its recommendation on orphan drugs in 2012, the Medical and Scientific Advisory Council of the U.S. National Hemophilia Foundation warned of "a danger that market exclusivity could potentially create a monopoly rather than allow for market competition that would ensure the widest possible access at the most affordable price." Dr. Powell emphasized the importance of flexibility so that individual patients can have the product of their choice, and of competition over market exclusivity.

Discussion

Dr. Marilyn Manco-Johnson contested Dr. Powell's statement that 30 years of hemophilia research with factor concentrates has been 100% safe, based on her participation in three long-acting FVIII studies, in which some patients who switched from factor therapy every other day to a once-weekly factor therapy have had major hemorrhages during the washout period when they stop prophylaxis. People with hemophilia voluntarily contribute enormously to research when they enter into clinical trials. While there have been no deaths nor extremely high rates of inhibitors, these patients risk and suffer adverse consequences in the good of the whole community. It is important to be cautious with the new products and advise patients that they may or may not work better than their current therapy. Regulatory agencies have a critical role in following data from multiple centres and assessing whether a product's safety and efficacy is in line with good clinical practice and expected outcomes.

Mr. O'Mahony said the EHC and NHF Medical and Scientific Advisory Council clearly have common concerns about market exclusivity and orphan drug designation. There could well be a two-year delay between when the new products are licensed in the U.S. and when they are licensed in Europe. It would be detrimental for one long-acting FVIII product and one long-acting FIX product to have a monopoly over the entire market. Efforts are being made to prevent market exclusivity from becoming a reality.

Interchangeability of Coagulations Proteins: The Treaters Perspective

MARIJKE VAN DEN BERG, MD, PHD, PEDIATRIC HEMATOLOGIST, DEPARTMENT OF HEALTH SCIENCE AND EPIDEMIOLOGY, UNIVERSITY HOSPITAL OF UTRECHT, THE NETHERLANDS

Dr. Marijke van den Berg gave an overview of the evolving safety paradigm for blood products, concerns related to immunogenicity and product switching, and considerations for the clinical development and use of the new generation of long-acting products and biosimilars.

Safety Paradigm

The development of factor concentrates over the past 30 years has been driven by the need for blood products, the impacts of the HIV epidemic and HCV in the blood supply on people with hemophilia, and the pursuit of increased blood safety. As a result of the blood safety and supply issues, hemophilia patients have become more actively involved in decision-making processes.

Over the years, hemophilia has seen a paradigm shift from supply and availability to a focus on safety, with complete safety as the ultimate goal. The concept of safety has expanded beyond transmissible pathogens to inhibitors, and immunogenicity is now the greatest concern. Key issues are how to define safety and the type of data needed prelicensure and at market authorization.

Risk of Inhibitors

Studies have found a low risk and incidence of inhibitors in previously treated patients (PTPs). A 2012 study by Alfonso Iorio and Michael Makris on factor concentrate switching and inhibitor development in hemophilia A noted that there is considerable debate as to whether plasma-derived and recombinant concentrates are associated with different risks of developing inhibitors, and found that although common in previously untreated patients (PUPs), inhibitor development is rare in multiply exposed, well-tolerized patients. A number of large PTP studies on recombinant products coming into the market have shown the inhibitor risk for PTP patients to be very low. There are also other risk factors including genetics, immunological response, and other individual characteristics. Much remains unknown about inhibitors and it is important to continue to be active in reporting inhibitor events in order to increase knowledge and understanding.

Product Switching

There are many good reasons for switching products such as: improved safety, fewer side effects, price, national contracts, smaller volumes, storage advantage, patient or family preference, and longer half-life. Reasons that patients or physicians may be reluctant to switch products include: a strong psychological link to one factor product, concern that switching leads to a higher chance of inhibitors, concern about transmissible pathogens, and ongoing debate on whether high-purity plasma and von Willebrand factor products have a lower risk for inhibitors. The Netherlands has a strong philosophy of unpaid donors and self-sufficiency and most older patients still use Dutch blood products; they are happy with their treatment and there is no safety reason to support switching them to another product.

A number of papers have been published over the past 25 years on the risk for inhibitors after switching products. In both PUP and PTP populations, the findings show no direct correlation with switching products nor a clear increase in inhibitors with the products that are now in the market. Still, there is much debate about whether certain products have a higher or lower immunogenicity risk. In 2003, a systematic review of the epidemiology of inhibitors in hemophilia A and the association between type

of FVIII product and inhibitor formation found a wide range of data. The review included a 1992 study that showed inhibitor development in 52% of patients with severe hemophilia on multiple plasma-derived products, and a 1990 study that showed inhibitor development in 5% of patients on a single plasma-derived product. Both studies, however, involved a small number of patients. A more recent systematic review in 2010 found that recombinant products have a higher inhibitor incidence rate. Problems with outcome definitions and lack of information on confounding factors remained; most importantly, studies on average are small.

Another study combined data from the retrospective CANAL Study involving patients with severe hemophilia A (FVIII <2%) at 14 centres born from 1990 to 2000 and followed until 50 exposure days and the RODIN Study on patients with severe hemophilia (FVIII <1%) at 29 centres born from 2000 to 2010 followed until 75 exposure days. Analysis of data from 921 patients with severe hemophilia A and factor levels below 1%, followed until 50 days, showed a similar definition of inhibitor. Clinically relevant inhibitors are defined as at least 2 positive titres above 0.3-0.6 BU/mL plus decreased FVIII recovery, while high-titre inhibitors are clinically relevant and have a peak titre of at least 5 BU/mL. Two positive tests on two separate samples are required to confirm the diagnosis. The cumulative inhibitor incidence for all PUPs with severe hemophilia A from 1990 to 2010 was 28.5%. There was no difference seen between type of plasma-derived products and type of recombinant products.

New coagulation factors will offer improved biosynthesis, prolonged half-life, and hopefully lower immunogenicity. The products fit the definition of biosimilar, i.e., a follow-on biological medicinal product whose active drug substance is made by a living organism or derived from a living organism by means of recombinant DNA or controlled gene expression methods. The European Medicines Agency has revised its overarching guideline on similar biological medicines and earlier this year published a draft for public consultation; the U.S. Food and Drug Administration has also released a series of guidances on biosimilars. The overall summary of the EMA's draft guidelines, which will be further debated later this year, are that clinical studies for large biosimilars should be deferred to studies on equivalence because a biosimilar is a biological medicine that contains a version of the active substance of an already authorized original biological medicine and the biosimilar demonstrates similarity to the reference medicinal product in terms of quality, biological activity, safety, and efficacy based on a comprehensive comparative exercise.

There are several factors to consider in the development of new products. While a new biosimilar or extended half-life product may be based on the same techniques, cell systems, cell lines and processes of a previous product, there is still a large knowledge gap on comparability. It is essential to prove that a biosimilar is really equivalent in all respects and, particularly, to confirm its safety aspects. FVIII and FIX biosimilars will require non-clinical and clinical studies that show biosimilarity to the innovator products. A 2012 study on time until inhibitor development after the introduction a new product by Kathelijn Fischer based on data from the CANAL Study showed that a substantial number of PUPs must reach the threshold of 50 exposure days to be able to compare the history and determine immunogenicity.

Clinical studies are critical to address safety. The knowledge gaps demand quality studies and non-clinical and clinical studies. Biosimilars must demonstrate the same safety profile to be considered interchangeable. Good competition and price is only possible when patients and physicians agree on the quality and safety of these new products. Comparable clinical data is needed but it will be very difficult to collect the data given the growing competition and considerable number of new extended half-life and biosimilar products about to enter the market, and small patient populations. The right balance between safety and feasibility is needed.

Prospective registries are important to post-marketing data collection. The European Haemophilia Safety Surveillance (EUHASS) Registry prospectively follows 20,000 patients at 84 centres in more than 20 countries, including Canada and Australia, and monitors adverse events. The European Pediatric Network for Haemophilia Management (PedNet) has established the PedNet Haemophilia Registry of PUPs, involving 30 centres from 16 countries. Patients are followed prospectively from birth onwards through the collection of all data concerning treatment, side effects, and outcomes of treatment. All patients will receive the new generation of products and patients newly diagnosed at the centres will be entered into the system.

It is utopian to expect all side effects of biological products to be known at marketing authorization. Patients, physicians, regulators, and industry have to explore other decision-making processes with regards to the new generation of products. Well-defined post-marketing registries should be obligatory for rare diseases to improve knowledge and safety. Patients and parents need to be informed of the limitations of the knowledge of these products and they have to become very actively involved.

Discussion

Declan Noone of the Irish Haemophilia Society said if the concept of biosimilarity and interchangeability are accepted, would it be possible in the future for a manufacturer to create a recombinant biosimilar product and enter the market without requiring clinical trials to prove biosimilarity? Dr. van den Berg said that in practice, biosimilarity is a contradiction in terms, because, in fact, similarity or interchangeability can only be proven when all the data from clinical studies available. More and more companies now realize it is preferable to form clinical studies in order to get competitive data about the quality of their products. Otherwise, physicians and patients are not really willing to switch to new products. There is currently a lack of knowledge in this area. Biologicals are much more complex than generic drugs, so it's critical to determine whether or not they are really interchangeable.

Dr. Jerry Powell said one of the major concerns in hemophilia is getting factor products to developing countries; 75% of the global hemophilia population live in the developing world and have little or no access to treatment with factor concentrates. This goal will be achievable much faster if clinical trials focus simply on demonstrating safety and efficacy, and not biosimilarity. Dr. Flora Peyvandi said the issue is to determine the minimum data required to get sufficient information on the safety of biosimilars in order to facilitate their entry to the market. She cautioned that even with the same recombinant product, there can be some differences from one lot to another. Mark Skinner added that even with good manufacturing practices, very small changes in the manufacturing process can make a very big difference. With biosimilars, patients and clinicians need to be informed about the benefits and trade-offs with different drugs. The common goal is to make safe and efficacious products more affordable and more accessible.

SESSION 5: MANUFACTURER UPDATES

CHAIR: ALAIN WEILL, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA

Scientists continue to advance innovative research and development of new and improved products for the treatment of inherited bleeding disorders, said Alain Weill. In this session, representatives from four pharmaceutical manufacturers presented their latest research and updates.

Clinical Development of Recombinant Factor VIII Fc Fusion Protein and Recombinant Factor IX Fc Fusion Protein

PAM FOULDS, MD, SENIOR DIRECTOR, GLOBAL MEDICAL AFFAIRS HEMOPHILIA, BIOGEN IDEC
ROBERT PETERS, PHD, SENIOR DIRECTOR, HEMOPHILIA RESEARCH, BIOGEN IDEC

Pam Foulds gave an overview of the pivotal data on Biogen Idec's long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) and recombinant factor IX Fc fusion protein (rFIXFc). Phase III studies on safety, efficacy, and pharmacokinetics have been completed and Biogen Idec has filed biologics license applications in the United States, Canada, Australia, and Japan.

The A-LONG Study was a global, multi-centre phase III clinical trial that evaluated the efficacy, safety, and pharmacokinetics of rFVIIIFc in previously treated patients (PTPs) with hemophilia A of diverse ages, races, and regions of the world. The study design included three different dosing regimens: individualized prophylaxis, weekly prophylaxis, and episodic therapy. Patients already on prophylaxis were allowed to choose any of the regimens; patients on episodic therapy could choose individualized prophylaxis or be randomized into weekly prophylaxis or episodic therapy. There were 165 patients enrolled, ages 12 and older; 111 patients completed at least 50 exposure days within the study. The results show that rFVIIIFc is effective in weekly prophylaxis, individualized prophylaxis, episodic therapy, and surgery. No inhibitors to rFVIIIFc were detected and no serious adverse events related to rFVIIIFc were reported.

In the individualized prophylaxis arm, patients were treated with 25-65 IU/kg of rFVIIIFc every three to five days. Dose and frequency were individualized to maintain 1% factor trough levels, based on individual pharmacokinetics, bleeding events, and decisions by the physician and patient. The median weekly dose was 78 IU/kg. About 30% of the patients were able to maintain 1% trough levels on a five-day dosing schedule. Sequential pharmacokinetic analysis was done on a subset of 28 patients who had been on Advate® prior to enrolment in the rFVIIIFc clinical trial. The rFVIIIFc pharmacokinetic results showed half-life extension by up to 19 hours compared to 12.4 hours for Advate®, reduced clearance, and increased time to 1%. Patients in this arm had low annualized bleeding rates; the median annualized bleeding rate was 1.6 bleeds.

In the weekly prophylaxis arm, patients were treated with 65 IU/kg of rFVIIIFc. Patients in this arm had slightly higher annualized bleeding rates than patients on individualized prophylaxis but close to 18% were bleed free; the median annualized bleeding rate was 3.6 bleeds. In the episodic treatment arm, bleeding episodes were controlled in a majority of patients with one infusion of rFVIIIFc; some required two infusions.

There are two ongoing clinical studies: a pediatric clinical study of PTPs under age 12; and the Aspire extension study of patients who have completed the A-LONG study. Biogen Idec is currently working with physicians and regulators to design trials for previously untreated patients (PUPs).

The B-LONG Study was a global, multi-centre phase III clinical trial that evaluated the efficacy, safety, and pharmacokinetics of rFIXFc in PTPs with hemophilia B. There were 123 patients enrolled, ages 12 and older; 55 patients completed at least 50 exposure days within the study. The study design included four treatment arms: weekly prophylaxis, individualized interval prophylaxis, episodic/on-demand therapy, and perioperative management.

Patients on weekly prophylaxis were treated with 50 IU/kg of rFIXFc, with dose adjusted to maintain factor levels. The median weekly dose was 45 IU/kg of rFIXFc. Patients on individualized prophylaxis were treated with 100 IU/kg of rFIXFc starting at every 10 days, with intervals adjusted to maintain factor levels. Dosing intervals in this group ranged from 10 to 14 days, with a median dosing interval of 12.5 days. Patients in the episodic therapy arm received rFIXFc on-demand treatment as needed for bleeding. The perioperative management arm included patients from all arms who underwent surgery. Sequential pharmacokinetic analysis was done on patients who had been on BeneFIX® prior to enrolment in the rFIXFc clinical trial. The rFIXFc pharmacokinetic results showed half-life extension by up to 82 hours compared to 34 hours for BeneFIX®, reduced clearance, and increased time to 1%.

The overall median annualized bleeding rate was 2.9 bleeds for patients on weekly prophylaxis arm, 1.4 bleeds for patients on individualized interval prophylaxis, and 17.7 bleeds for episodic treatment. In the individualized interval prophylaxis arm, the median dosing interval during the last 6 months of the study was 14 days. Control of bleeding was assessed in all patients who experienced a bleeding episode during the study; 90% of bleeding episodes were controlled by a single injection of rFIXFc. There were 14 surgeries in the study; bleeding in all surgeries was very well controlled. The results show that rFIXFc is effective in weekly prophylaxis, individualized prophylaxis, on-demand therapy, and surgery. No inhibitors to rFIXFc were detected. One serious adverse event, obstructive uropathy in the setting of hematuria, was reported and assessed to be possibly related to rFIXFc; the patient continued rFIXFc treatment and the issue was resolved. The pediatric clinical study is still ongoing, and a PUPs study is currently in the design phase.

Biogen Idec is working very closely with Swedish Orphan Biovitrum (SOBI) on the development and commercialization of these long-acting recombinant factor products.

FVIII Half-life Extension: Possibilities for the Future

Robert Peters described some future possibilities for FVIII half-life extension. In addition to Fc fusion technology, there are currently several long-acting FVIII therapies being assessed in clinical trials, all based on pegylation technologies (glyco-pegylation, cysteine variant-pegylation, amino group-pegylation). According to Phase I and IIa study results, these therapies all provide half-life extension of about 1.6 times and will make a significant clinical difference in the management of hemophilia A.

It has long been known that VWF has a protective role for FVIII; if FVIII does not bind with VWF, half-life is dramatically shorter, and FVIII is susceptible to proteolysis and rapid clearance from circulation. VWF has a limiting effect on FVIII half-life extension as FVIII-VWF binding interaction couples FVIII to be cleared by the VWF clearance pathway. This is evident in the maximal half-life of about 16 hours being achieved in clinical trials with the long-acting FVIII therapies, which is approximately the same as VWF half-life.

Investigators sought to cleave the FVIII molecule from the VWF molecule as a way to achieve further half-life extension. Using Fc fusion technology, a segment of the D'D3 region of VWF, which is known to interact with the C1/C2 region of FVIII, was appended to the free Fc arm of the FVIII Fc monomer to create intra-molecular interaction. The binding of the D'D3 region to the C1/C2 region in vitro successfully prevented the interaction with the physiological VWF and also provided some of the protection of the full-length VWF.

Half-life extension has also been achieved with pegylation technologies, which use chemical ligation to increase the hydrodynamic radius of conjugated proteins and may shield the FVIII molecule from clearance receptors and/or protease cleavage.

Investigators also sought to further extend half-life using XTEN technology (Amunix) to generate unstructured protein sequences that increase the hydrodynamic radius of fusion proteins. XTEN is fully recombinant and allows precise control of composition, length and placement of insertions, including multiple insertions, without chemical modification. XTEN contains natural amino acids that are ultimately metabolized into amino acids in vivo. Preclinical experiments in hemophilia A mice showed improved pharmacokinetic properties when appended to therapeutic peptides and proteins, with more than twofold increase in half-life.

Discussion

David Page said that for a long time BeneFIX® has been described as having a half-life of 19 hours but it is now said to have a half-life of 33 hours; other products seem to similarly to be described as having longer half-life as well. This is extremely confusing and challenging in terms of teaching patients about how half-life works. The three manufacturers developing FIX products need to all use the same time point and assess at the same time point, one closer to time of infusion. Dr. Foulds acknowledged that different time points of 48 hours and 96 hours are being used and that it is important to use the same time point to obtain an equal understanding of half-life.

Dr. Flora Peyvandi said clinicians are facing a lot of difficulties in Europe due to the European regulatory requirement for pediatric clinical trials, and asked about the timeframe required for pediatric studies. How long will it take for the 20 children with hemophilia B and 50 children hemophilia A in Biogen Idec's clinical study to reach 50 exposure days, and how many exposure days were reached by adult patients before starting the pediatric trial? Dr. Foulds said the European regulations are challenging; Biogen Idec has been working with patient and advocacy groups to address the pediatric trial issues with the EMA. A key challenge has been retaining patients through to completion of the study. One big constraint in the PUPs trials is the need to obtain patient consent before filing for marketing authorization.

Dr. Alok Srivastava noted that an episodic treatment arm is not a regulatory requirement. He asked whether, going forward, trial design of future studies should still include an episodic arm. Dr. Foulds explained that the Biogen Idec clinical trials were part of a multi-country study and included many developing countries where patients are still on episodic therapy. However, no patients are randomized into the episodic arm; enrolment is based on patient and physician choice.

Baxter Healthcare – Innovation in Hemophilia?

ARMIN REININGER, MD, PHD, HEAD, GLOBAL MEDICAL AFFAIRS HAEMOPHILIA, BAXTER INNOVATIONS

The ultimate goal in hemophilia is a bleed-free world in which patients have no joint bleeds and are able to live truly normal lives—however, the community is still a long way from achieving this vision, said Dr. Armin Reininger. Progress needs to be made step by step, and one patient at a time, and requires true collaboration across the hemophilia community.

Data on lifetime joint bleeds, joint, scores and joint health show that very few people with hemophilia go through life incurring no joint damage. Only those who had zero to two bleeds over their lifetime had normal joints and normal joint scores as determined by physical examination, X-ray, and MRI. Evidence shows moderate damage with three joint bleeds over a lifetime, and substantial damage with four or more joint bleeds over a lifetime. While there is much discussion about annualized bleeding rates, for normal joint health, only a very low number of bleeds over a lifetime is acceptable.

Pharmacokinetics

Pharmacokinetics vary widely among patients and with age. Published data show that among patients aged 12 to 65 treated with a dose of 30 IU/kg of FVIII concentrate, half-life can range from 8.8 hours to 15.4 hours, and it can take from 46 to 103 hours for patients to reach a 1% trough level. Therefore, weight-directed dosing does not provide very satisfactory bleed protection. Pharmacokinetics can be used to optimize bleed protection by adjusting dosing to half-life; however, patients must undergo pharmacokinetic analysis in order to know their half-life.

In prospective studies on Advate®, pharmacokinetic evaluation samples taken from 2,035 patients showed that pharmacological response to FVIII concentrate varied based on individual pharmacokinetic characteristics. FVIII plasma levels vary between patients at different time points after infusion, ranging from 30% to 250% at the starting point, and with a large variance over 48 hours. FVIII plasma levels in the general population are normally in the range of 60% to 200%.

Data from prospective clinical studies on Advate® for routine prophylaxis published in 2009 showed a wide variance in FVIII use (IU/kg per year) in 34 patients on pharmacokinetic-tailored prophylaxis in order to maintain at least 1% trough levels; every patient used a different amount of FVIII concentrate to achieve a 1% trough level. It is well known that patients with different lifestyle and activity levels may need different FVIII trough levels. Physical activity level is clearly linked to good health in the general and hemophilia populations alike. Patients may need higher trough levels to participate in sports in a regular manner; this requires that the patient know how to dose for additional protection. These large variances and individual differences can be addressed with innovative approaches.

Analysis of patient annual bleed rate compared to trough level showed that some patients with low trough levels had low annual bleed rates; however, other patients with low trough levels had higher bleed rates. Similarly, there were patients with high trough levels who had low annual bleed rates while others had higher bleed rates. Some patients probably need a lot more factor for their annual bleed rate to be brought down to an acceptable level.

Dr. Reininger outlined a framework for tailoring treatment. For patients with above 3% trough levels and low annual bleeding rate, the goal is to optimize dosing to decrease utilization while maintaining effectiveness. Patients with above 3% trough levels and high annual bleed rates should be given pharmacokinetic-tailored therapy based on individual trough level targets. For patients with below 3% trough levels and low annual bleeding rates, treatment should be maintained at its current level.

Patients with low trough levels and high annual bleed rates should have their dosing increased to a target trough level to prevent bleeding.

Data from April 2011 to March 2012 published by the United Kingdom Haemophilia Centre Doctors' Organisation showed an average annual joint bleed rate of 2.8 bleeds for pediatric and adolescent patients, and an average annual joint bleed rate of 5 bleeds for patients aged 18 and older.

Real-world data supports the efficacy and annual bleed rates reported in clinical studies. The Advate® PASS meta-analysis looked at five studies done with Advate® in the last 10 years and documented real-world clinical practice using Advate® in 1,140 patients in the United States, Australia, Japan, and 12 countries in the European Union. Results showed that 560 patients on continuous prophylaxis (twice weekly or more) during the study had a median annual bleed rate of 1.67 bleeds. Treatment can be push further in the direction of zero bleeds, Dr. Reininger said.

The Advate® AHEAD study is a long-term Advate® joint outcome registry that is collecting data from both the clinical and home treatment settings. The primary objective is to track joint scores in relation to bleed events, annual bleed rates, prophylaxis, and on-demand therapy. The registry allows the comparison of individual centre performance to blinded overall study data. So far, over 500 patients from EU countries have been registered.

These studies indicate that pharmacokinetic-tailored therapy is superior to dosing by weight. However, more evidence and data is needed. This type of innovation is bringing the hemophilia community closer to the goal of a bleed-free world, he concluded.

Discussion

Dr. Marijke van den Berg said extensive data collected in the U.S. and Europe indicates that the age of starting prophylaxis is very important to joint outcomes. One issue with annual bleed rates pertains to whether or not patients are reporting their bleeds accurately.

Manufacturing Process for the New Recombinant Factor VIII Turoctocog Alfa

KNUD VAD, PHD, GENE TECHNOLOGY EXPERT, NOVO NORDISK, DENMARK

Novo Nordisk's new recombinant factor VIII turoctocog alfa product, NovoEight®, is based on advanced protein and purification technology and has been designed for reliability, safety and portability for people with hemophilia A. An extensive Phase III clinical trial was initiated in 2009 with more than 200 previously treated patients (PTPs) from all age groups, and a clinical trial in previously untreated patients (PUPs) is now underway.

FVIII is a large molecule with more than 2,300 amino acids in its endogenous form. It is very fragile and sensitive to degradation and requires rapid binding to plasma von Willebrand factor (VWF)—this is the key challenge in developing FVIII molecules. The turoctocog alfa molecule, NovoEight®, is a B-domain truncated recombinant FVIII molecule with 1,445 amino acids. The B-domain is known to be important for FVIII secretion in perfusion cell culture and has no action in the coagulation cascade.

There are many steps in the NovoEight® manufacturing process, beginning with FVIII gene expression in a Chinese hamster ovary (CHO) cell line transfected with a vector containing the turoctocog alfa expression cassette; followed by capture of rFVIII from the cell culture media; then purification through virus elimination, chromatographic, and immunoaffinity steps; and, finally, production formulation.

The FVIII B-domain is truncated to a segment of 21 amino acids and engineered using glyco-pegylation. CHO cells were selected for their expression capability for human proteins; it is a well-established cell line for production of biopharmaceutical products and has a reduced risk for carrying human pathogens. Fermentation is a key step in the production process and must be conducted with great care to prevent degradation of the FVIII molecule. Full tyrosine sulphation has been achieved to ensure optimal VWF binding. The viral inactivation steps include detergent treatment, anti-rFVIII immunoaffinity chromatography and anion-exchange chromatography, nanofiltration with a 20 nm pore-size filter, and size exclusion chromatography. The process results in a highly purified product.

In Phase III trials which included previously treated adults and children with severe hemophilia A, NovoEight® demonstrated good efficacy in preventing and treating bleeds, no inhibitor development, and all patients in the surgery trial were efficiently treated.

Novo Nordisk has filed marketing authorization applications for NovoEight® in Europe, the United States, Japan, and Switzerland. The Committee for Medicinal Products for Human Use of the European Medicines Agency has adopted a positive opinion on NovoEight® and recommended its marketing authorization for the treatment and prophylaxis of bleeding in patients with hemophilia A. Final marketing authorization in Europe and the United States is anticipated in the coming months.

Discussion

Dr. Flora Peyvandi noted that Novo Nordisk is also developing a glyco-pegylated recombinant FIX molecule but encountered problems with the extension of the clinical study. This was a challenge for clinicians treating patients with rFIX-GP, who had to be told after many exposures that their trial and therapy was discontinued. This is why market exclusivity is a big challenge for clinicians and patients, she said.

Dr. Vad said there were issues related to upscaling the manufacture of rFIX-GP due to the failure to double the fermentation capacity in order to maintain sufficient supply of rFIX-GP for the extension trial. The extension trial was unfortunately discontinued until after the pivotal trial, which has now been completed.

CSL Behring: Committed to the Bleeding Disorders Community

MATHIAS JUERS, MD, DIRECTOR, MEDICAL AFFAIRS, COMMERCIAL DEVELOPMENT COAGULATION, CSL BEHRING

CSL Behring is currently pursuing research and development of new recombinant factor therapies for bleeding disorders which will confer extended half-life, lower immunogenicity, and reduced bleeding frequency. Products in the development pipeline include recombinant single-chain FVIII and recombinant FIX, FVIIa, and VWF fusion proteins. In addition, CSL Behring's plasma-derived FVIII/VWF concentrate (Voncento®) was granted marketing authorization by the European Medicines Agency earlier this year.

Scientists face several challenges in developing coagulation factors with extended half-life. They must identify the optimal half-life extension method for both treatment of acute bleeds and long-term prophylaxis; achieve half-life extension while also preserving efficacy and biological activity; and ensure safety and tolerability. CSL Behring's recombinant factor fusion proteins are engineered using albumin fusion technology to extend the half-life of the circulating molecules. Albumin is a protein commonly found in high abundance in blood plasma. It is a large carrier protein with a long half-life of about 20 days and considered to be immunologically inert.

Recombinant FIX Fusion Protein

A preclinical study compared recombinant FIX fusion protein (rFIX-FP) and recombinant FIX (rFIX) pharmacokinetics in hemophilia B dogs, given at a dosage of 100 IU/kg. Results showed that rFIX-FP has a significantly increased half-life of about tenfold. Phase I and Phase I/II studies on the rFIX-FP have been completed.

The 2010-11 Phase I study evaluated the safety and pharmacokinetics of rFIX-FP using dose escalation in patients with severe hemophilia B. The pharmacokinetics of rFIX-FP was assessed at each dose level (25, 50, and 75 IU/kg); and the pharmacokinetics of a single 50 IU/kg dose of rFIX-FP was compared to the same dosage of the patient's previously administered recombinant or plasma-derived FIX product. The study results showed a significantly improved pharmacokinetic profile compared to currently available FIX products, with about 44% higher incremental recovery, fivefold increased half-life, sevenfold larger area under the curve, and sevenfold slower clearance. Extended half-life of 5% trough levels at 7 to 14 days offers the possibility to derive a treatment regimen based on infusion once every week to two weeks. rFIX-FP was well tolerated with no serious adverse events, rFIX inhibitors, or rFIX-FP antibodies reported.

A Phase I/II study in Bulgaria and Israel evaluated the long-term safety, efficacy, and pharmacokinetics of rFIX-FP administered as on-demand therapy and weekly prophylaxis, and yielded results comparable to the Phase I study. All the patients in the prophylaxis arm maintained weekly prophylaxis with rFIX-FP throughout the study (37 to 48 weeks). All bleeding episodes were treated with two or fewer infusions. Phase II/III adult and pediatric studies to evaluate the safety, efficacy, and pharmacokinetics of rFIX-FP are now underway. A combined approach looking at both efficacy and pharmacokinetics will drive the future of factor therapies.

Recombinant VWF Fusion Protein

A preclinical study compared recombinant von Willebrand factor fusion protein (rVWF-FP) and plasma-derived VWF in rabbits, given at a dosage of 150 IU/kg. Results also showed significantly extended half-life.

Recombinant FVIII Single Chain Molecule

The FVIII single chain molecule **(**rVIII-SingleChain) is based on covalently connected heavy and light chains, which enhances molecular integrity, improves FVIII stability, and promotes faster and more efficient binding to VWF. The rVIII-SingleChain molecule displays a strong affinity for VWF. The FVIII/VWF complex plays an important role in the physiological activity and clearance of FVIII and has been shown to have an influence on the presentation of FVIII to the immune system. There is ongoing discussion on how VWF potentially reduces the presentation of FVIII antigens during immune tolerance induction therapy. Preclinical studies in hemophilia A mice showed a significant area under the curve and potential half-life extension.

Recombinant VIIa Fusion Protein

A recombinant FVIIa fusion protein (rVIIa-FP) is being developed for the treatment of patients with hemophilia who have FVIII or FIX inhibitors. The Phase I study evaluated safety and pharmacokinetics in 40 patients using dose escalation (140, 300, 500, 750 and 1,000 mcg/kg) and has been completed. There was no serious adverse events, and one mild adverse event related to pain and hardening of the vein at the injection site. Half-life at the highest dose (1,000 mcg/kg) was about 8.5 hours, which supports on-demand dosing.

In summary, albumin fusion is an efficacious and very safe method for the extension of half-life of coagulation factors, as demonstrated by preclinical and clinical data, and could offer significant benefits to people with hemophilia, including greater efficacy, extended half-life, reduced bleeding frequency, and less frequent dosing.

CLOSING REMARKS

ALAIN WEILL, PRESIDENT, WORLD FEDERATION OF HEMOPHILIA

To mark the its 50th anniversary this year, the World Federation of Hemophilia has produced a short video series highlighting the work of the organization. The latest video in this series, called "Improving Treatment Safety and Supply," was screened at the closing plenary.

The video featured hematologist Bruce Evatt, director of the Division of Blood Disorders, Centers for Disease Control and Prevention, during the HIV/AIDS crisis in the 1980s, describing the devastating epidemic of AIDS within the hemophilia population in the United States, Europe, and other parts of the developed world due to contaminated blood products. This tragedy, along with the subsequent discovery of hepatitis C in the blood supply, led to resolve in the hemophilia community to remain vigilant to ensure the safety and supply of hemophilia treatment products. At the same time, there was demand for increased availability of safe and affordable treatment products from patients in the developing world, where the majority of people with hemophilia have no access to treatment with factor concentrates. The first WFH Global Forum was held in 2000 to bring together governments, regulatory agencies, patients, and treaters to exchange perspectives on global blood safety and supply issues. The WFH's work in this area has evolved over the years and has contributed to a safer blood system for everyone.

In closing remarks, Alain Weill acknowledged the important contributions of David Page as chair of the WFH Blood Product Safety, Supply and Availability Committee from 2000 to 2012, who then received a lengthy standing ovation. Mr. Weill thanked the speakers for their stimulating scientific presentations and participants for the engaging discussions, and the Global Forum sponsors for their vital support.

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