

Promising new therapies for hemophilia

GREAT ADVANCES in hemophilia treatment are on the horizon. New therapies in development show exciting potential to improve treatment outcomes and quality of life. From pegylated liposomes, to synthetic antibodies that mimic factor VIII, and evolving treatment for patients with inhibitors, Tuesday's medical session comprised absorbing presentations on novel therapies for hemophilia.

Jack Spira of the Netherlands and Jerry Powell of the US described results from early clinical trials on recombinant factor VIII (rFVIII) formulated with polyethylene glycol-liposomes in patients with severe hemophilia A. Early trials with the pegylated liposome (BAY 79-4980) show a considerable prolongation in bleed-free periods following prophylactic infusion, with the first infusion bringing 13 days of protection compared to seven days on rFVIII, Spira said.

All infusions were well tolerated and inhibitor tests were negative. Results suggest the possibility of once-weekly prophylaxis, which will be explored in

Phase III trials. "Such a regimen would positively impact treatment by improving patient compliance and reducing complications such as long-term joint damage," Spira said.

Midori Shima of Japan presented early, but fascinating, research on the development of FVIII mimetic antibodies. By modulating the interaction between factor IXa and factor X, researchers at Nara Medical University have developed a bispecific antibody that mimics FVIIIa function. In an in vitro experiment, the addition of bispecific antibody to FVIII-deficient plasma demonstrated shortened clotting time, and did not interrupt FVIII activity — suggesting that their effects are additive, not competitive, Shima said.

The audience also heard research findings on a FVIIIa and FX mixture that offers sustained hemostatic potential and lower thrombogenicity. Kinetic analysis showed that FX gives a strong thrombin potential to FVIIIa, and enhances its bypassing activity. "We believe this mixture product will be the third option in

addition to the established bypassing agents, rVIIa and activated prothrombin complex concentrates," said Kazuhiko Tomokiyo of Japan. The clinical trial of the mixture product will be started later this year.

A pharmacokinetic study presented by Tom Abshire of the US compared a recombinant porcine FVIII (OBI-1) with Hyate:C for people with hemophilia inhibitors to human FVIII. In animal trials, OBI-1 appears to be efficacious, with immunogenicity, peak Bethesda titer, and antibody persistence similar to Hyate:C. ●

Prospective studies trace inhibitor development

PROSPECTIVE CLINICAL TRIALS are gradually shedding light on the genetic and environmental factors that contribute to inhibitor development, according to panelists in a *Meet the Experts* session Tuesday afternoon.

Jan Astermark of Malmö University Hospital, Sweden, reported on the Hemophilia Inhibitor Genetics Study (HIGS), a three-phase project aimed at identifying host genetic factors linked to inhibitor development in people with severe hemophilia A. Its secondary objective is to identify environmental factors that might heighten the risk of developing inhibitors.

The HIGS will begin with a whole-genome scan of classic sibling pairs, including affected pairs (ASPs) where

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While a volunteer observes, a patient administers his own treatment

IN THE HALLS

What did you find most interesting at this congress and what will you do in the next months to follow up on what you've learned?

The presentations on women's bleeding disorders were most interesting to me. My country has more than 900 hemophilia carriers, 30 per cent of whom have bleeding problems. I am eager to communicate the information on new issues, treatments, and discoveries to medical professionals as well as patients. – COLOMBIA

The management of inhibitors was most impressive. As a pediatric specialist in hematology, the next step for me will be examining inhibitor treatment in a controlled study. Otherwise we will never know precisely how patients respond differently to treatments and the best way to treat them. – GERMANY

Our organization is quite new so we face many challenges on governance. When we return, we hope to put lessons learned about building a strong national organization into action with leadership training at the local and provincial levels, and lobbying and media relations in order to improve hemophilia care and reach out to undiagnosed patients, especially in rural areas where there is no medical treatment. – CHINA

The scientific content of the Congress has been very good and it has been valuable to meet members of the hemophilia care community, as well as people with hemophilia from different nationalities under one roof. Our team is looking forward to better understanding the molecular basis of inhibitor development and will use information from this conference to elaborate our cohort study of patients with inhibitors. – INDIA

Field study seeks evidence to support routine use of ice

AN INITIAL STUDY on the benefits of ice in the first hours after a bleed generated interest and hope at yesterday's session on *Using Scientific Evidence to Guide Clinical Decisions*, despite the sharply limited number of participants who conformed with the research protocol.

"This is the first attempt I'm aware of to objectively measure the immediate effects of ice," a participant told panelist Ethelwyn Remmers of Pretoria Academic Hospital, South Africa. She encouraged Remmers to continue her work and extend it to other centres, noting that the question of whether ice actually reduces bleeding "is not well answered."

While widespread experience shows that ice reduces swelling and pain in a bleeding joint, Remmers said there is no clear scientific evidence to support the practice. With this in mind, Remmers set up a protocol for a randomized study involving people with congenital

hemophilia A or B whose bleeding episodes had occurred less than 24 hours prior to evaluation.

Long travel distances in South Africa meant that only two patients could meet the criteria. Both showed reduced swelling after treatment with factor concentrates and intermittent applications of ice. One of the two reported a moderate reduction in pain.

Goris Roosendaal of the University Medical Centre in Utrecht, The Netherlands, reported on an in vivo animal study of articular cartilage response to bleeding and weight bearing. Working with beagles aged 0.7 years, 2.4 years, and 7.7 years, the researchers found that joint damage due to injected blood was most severe in the youngest group. The combination of hemorrhage plus joint loading resulted in progressive, degenerative damage, though Roosendaal warned that the results were only suggestive for human patients. ●



More than 70 volunteers from Vancouver and Canadian Hemophilia Society Chapters across the country helped make Hemophilia 2006 World Congress a roaring success.

Balancing the advantages and disadvantages in approaches to venous access

CENTRAL VENOUS access devices (CVAD) should be used only when absolutely necessary because of complications associated with their use. While they can facilitate hemophilia management, peripheral veins should be the delivery mode of choice whenever possible,

especially in children, and CVADs should be removed as soon as therapeutically possible.

Victor Blanchette of the Hospital for Sick Children in Toronto cited data from a multi-centre meta-analysis of CVADs that tracked mostly pediatric patients

in several centres around the world. The most significant complication associated with their use was infection, particularly staph epidermidis and staph aureus. The pooled infection rate was 0.66 infections per 1,000 CVAD days. Patients under six had infection rates more than double older children, and the risk of an inhibitor increased by 67 per cent when a CVAD was present.

Thrombosis is another significant complication. "A lot of people thought that, because of the hemophilia, thrombosis couldn't occur," Blanchette said. In fact, a recent study at the Hospital for Sick Children found deep vein thrombosis (DVT) in 81 per cent of young patients with CVADs, despite that fact that only one-quarter of them showed dilated vessels on the anterior chest wall, which are most commonly associated with DVT.

Blanchette predicted that as screening for DVT becomes more commonplace, it will lead to increased CVAD removals. He recommended both ultrasound and venograms to screen for DVT, and beginning surveillance by three or four years of age. "People should be much more aggressive about getting these devices out and switching to peripheral venous access."

The use of arterio-venous fistulas (AVF) appears to be a good option in cases where prophylaxis or immune tolerance therapy require frequent infusion, Blanchette said. An Italian study has found AVF allowed for successful home treatment in 26 of 27 cases, with relatively no associated infection and relatively little thrombosis.

Eadoain O'Shea, a hemophilia nurse from Dublin, Ireland, presented case studies of two adult patients with AVF. Although there were complications and both AVFs eventually failed due to stenosis, the patients were extremely enthusiastic about the advantages. "It's important to be creative in care and treatment, and find the right fit for the individual patient," she said. ●



Panelists in Tuesday's Meet the Experts Session on inhibitors shared potential solutions from clinical trials

Prospective studies *continued from front page*

both brothers have developed inhibitors and discordant pairs (DSPs) in which one of them has not. The genome scan will cover 300 to 800 markers, with the intent of identifying candidate genes and regions that the affected pairs share but the discordant pairs do not.

In the second phase, the study team will conduct a transmission disequilibrium test with small family units with one affected child. In this phase, population substructure will be unimportant: knowing that each heterozygote parent will contribute one allele to the child, the researchers will count the alleles transmitted to the affected child. The alleles associated with inhibitor development will be shared more often than would otherwise be expected.

The HIGS will conclude with a population-based study to confirm the findings of the first two phases.

Astermark said the HIGS might draw

insight from the International HapMap Project, an effort to describe common genetic variations among Asian, European, and African populations.

W. Keith Hoots of Houston Medical School, us, traced the development of the Hemophilia Inhibitor Previously Untreated Persons Study (HIPS), an international, multi-centre trial that will track the natural history of inhibitor development from the early days of life.

The study population will consist of previously untreated infants with baseline factor VIII levels below one per cent who have received fewer than three units of FVIII or any other blood product. Hoots stressed that patients who are candidates to develop inhibitors "are precious resources, and we really need to work collectively so that the information gleaned from such studies is maximized, without putting undue burden on individual participants to be in multiple studies." ●

PROGRAM UPDATES

The Awards Presentation Ceremony honouring members of the global hemophilia community will take place at 1:00 today in Ballroom C.

The Farewell Banquet is sold out.

CME credits: Please present yourself at the registration desk to receive your CME certificate. We will require your name, medical license number, and signature.

SESSION CHANGES

● Thursday, May 25

D1.3 – Treatment of Inhibitors from a Multidisciplinary Perspective

The session will begin with a 20-minute video presentation by Guy Henri Godin on a patient with inhibitors who went through two major surgeries.

D1.6 – MUSCULOSKELETAL Update on Clinimetric Instruments

Sharon Funk will co-present the *International Joint Health Score: Clinical Scoring System*, with Pam Hilliard.

D3.1 – MEDICAL European Study of Quality of Life

Lazlo Nemes, Paul Giangrande, and Wolfgang Schramm will present *Clinical Status and the Prevalent Treatment Modalities of Adult Hemophiliacs in Europe*, with Alessandro Gringeri. Margit Serban will present *Clinical Status and the Prevalent Treatment Modalities of Children and Adolescents in Europe*, with Rolf Ljung. Sylvia von Mackensen will present *Evaluation of Quality of Life in Children/Adolescents and Adults with Hemophilia in Europe*, with Monika Bullinger.



The next Congress may be two years away, but the excitement is already palpable at the Hemophilia 2008 booth (pictured above). Staff from the Hemophilia Society of Turkey sing the praises of Istanbul – a meeting point for people from different cultures for thousands of years. What better place to bring the vision of treatment for all than this legendary city where east meets west? See you in 2008 in Istanbul!

SESSIONS TO WATCH FOR

D1.1 Using gene transfer in the treatment of hemophilia is realistic and achievable, despite significant obstacles that have been identified in the past 15 years of pre-clinical research. This year's *Arosenius Lecture* will explore current obstacles and the lessons learned from previous research that might help overcome them. In addition, delegates will hear the latest studies on clinical gene transfer for hemophilia B, and emerging cellular and genetic approaches for viral and non-viral gene delivery systems. *Presenters are David Lillicrap, Katherine High, and Thierry VandenDriessche. The lecture will take place today at 11:00 in Exhibit Hall A.*

D3.2 Different approaches work in different parts of the world when pressing for the introduction or improvement of hemophilia care. This afternoon's *Lobbying Strategies* session will share experiences from New Zealand, Bulgaria, and Iran, and will include an overview of some good strategic approaches that have met with success in the past. *Presenters are Brian O'Mahony, Jordan Nedevsky, Shirin Ravanbod, and Mike Carnahan. The session will take place at 4:30 in Meeting Room 11/12.*

D2.2 Both the management of infectious disease in hemophilia patients, and the possibility of pathogen transmission through transfusion of blood products continue to be serious issues in hemophilia management. Today's *Infectious Disease Update* will review current and emerging therapies for the management of HIV and HCV coinfection, long-term treatment complications, and the possibility of the transmission of other pathogens. *Presenters are Christos Tsoukas, Jenny Heathcote, and Roger Dodd. The session will take place at 2:30 in Meeting Room 1.*

D2.4 Fear of the possible consequences of dental treatment often keeps families from getting appropriate dental care for people with hemophilia, particularly children. While oral and dental care continues to be a challenge, the *Restorative Dentistry* panel will present approaches for evaluating and designing treatment strategies for in dental management and oral health for people with hemophilia in both emerging and developed countries. *Presenters are Lionel Cudzinowski, Ayyaz Khan, and Alfredo Conejo. The session will take place at 2:30 in Meeting Room 8.*