EUROPEAN
HAEMOPHILIA CONSORTIUM

newsletter • June 2005

CONTENT

WISHING AND **HOPING**

The 18th EHC annual meeting gave two important words to all participants.

"Wishes" for better and safer treatment, as well as adequate product supply for all; and "hoping" for patient futures without bleedings, pain, joint problems and disabilities. At the excellent gala dinner on Saturday evening, a clear picture of what can be achieved with good treatment was clearly demonstrated with so many people dancing to the sound of Spanish rhythms. The scene followed two days of talking about being different, being able to do sports, dancing and getting around, and provided an optimistic view of the next generation of people with haemophilia. During the evening, watching everybody dance, in the way, that I have never been able to, this old lyric from a song by the Kinks came into my mind:

"Here's wishing you the bluest sky,
and hoping something better comes tomorrow."
"It's really good to see you rocking out
And having fun,
Living like you just begun.
Accept your life and what it brings.
I hope tomorrow you'll find better things."

MEETING ...

... at the Mediterranean Sea.

This years meeting took place in Hotel Mercure, wonderfully situated on the harbour of La Grande Motte, directly by the Mediterranean Sea near Montpellier. The number of participants exceeded 200 from more than 26 countries, the largest number ever. Welcome addresses were given by the President of the French Haemophilia Society, Edmond-Luc Henry, and Chairman of the EHC, Dr. Hubert Hartl, both of them thanking the organizers and sponsors of this meeting.

FRIDAY MORNING **LECTURES**

Haemophilia Treatment Update

Dr. Y. Laurian gave an excellent overview of the current status and development in new treatments for haemophilia. He led his presentation by asking the audience whether the European haemophilia community was now facing a choice: "access to recombinant products for all, or low cost prophylactic treatment for all?" and he made the suggestion that treatment with higher cost recombinant products may result in the risk of shortage in other countries.

Dr. Laurian then provided an update on the progress of gene therapy, where there are new good animal results, but human gene therapy is still at early clinical trial stage. The result is that current products may stay on the market for a further 10-15 years. In terms of new treatments, he stated that areas of development include factor concentrates with a longer half-life, products that decrease the risk of inhibitors and alternative routes of administration, by subcutaneous or oral ways. He reminded the audience however, that it takes 5-10 years to develop new drugs.

During the discussion, a question about who chooses the future direction of treatment development was raised, and in response, it was highlighted that future developments would differ between countries depending on their GDP/development levels. The question was therefore posed, within a limited budget, would the audience prefer to have 10.000 units of recombinant FVIII or 30.000 units of plasma derived product, if the price were the same?

Sports

Dr. J.F. Schved reported on a sport survey among 80 patients with haemophilia. Of those surveyed, 70% performed some kind of sport, including swimming, cycling, walking, table tennis etc, with less than 5% doing contact or high risk sports such as rugby, wrestling and skateboarding.

Dr. Schved noted with surprise that 66% were on on-demand treatment and not taking infusion before sport. He also noted that 42% had experienced some kind of sport accident, with the lowest rate recorded in swimming, where only one accident was reported.

The benefits however, of doing sports were clear, resulting in stronger muscles, reduced haemarthrosis, and an increased feeling of well being derived from being with others, making friends and the development of team spirit. It was also noted however, that people with haemophilia might experience fear from the family, and/or rejection by others because of their lack of knowledge or difficulties in following a training programme.

In the following workshop, it was agreed, that a careful evaluation of the patients condition, severity of disease and current treatment would need to be performed, and the risks associated with the sport assessed. It was considered very important that a patient is given realistic information regarding the risks associated with the choice of sport. It was also noted however, that many sports can be done at a high competitive level without risk of accidents, and that people with haemophilia should continue to be encouraged to do sports, which are considered as low risk.

Insurance

A. Marion gave a very interesting and very clear speech about an otherwise unexciting topic – insurance.

A. Marion explained that contrary to industrial production, where the production sequence starts at the raw material purchase, goes onto the production stage and then ends with the selling of the product at a known price, an insurer has a different sequence. As an insurer, one has to first sell the product – the insurance – and then later wait and see if the premium has met the cover payments.

Insurance companies work with risk tables, where the given risks of death, accident, retirement or other events are calculated, and the insurance premium is calculated from this. Since such tables are made on an average population, it is very difficult to estimate the risks of a small group of patients with a rare disease.

For patients with haemophilia there are several possibilities:

- No insurance at all, because the risk assessment is too high or not known.
- Insurance only available with an increased premium.
- Group insurance - where several patients join in a mutual insurance fund.
- Insurance with reservations that do not cover certain situations.

In the discussion following the presentation, it became clear, that insurance for people with haemophilia is difficult because in many cases statistics and risk tables do not exist for this group of persons. It was concluded that registries about haemophilia death rates and sickness are needed to show the exact risks, so that insurance companies can estimate reasonable insurance conditions.

SATELLITE **LUNCH SYMPOSIUM**

Presentation of the new Advate® recombinant Factor VIII

In this symposium, sponsored by BAXTER, the experience with their new Advate® recombinant Factor VIII was presented.

Dr. Chehadeh began the symposium by providing an overview of the development in factor products in relation to viral and pathogen safety, beginning with hepatitis B screening of blood donors in 1975, through to first inactivation methods in 1980, testing for HIV and HCV, recombinant products from 1992 and PCR testing of plasma from 1995. Dr. Chehadeh however still pointed out that potential risks continue to exist from unknown and emerging pathogens and viruses – most recently illustrated by the emergence of West Nile virus, East Asian bird influenza virus, and also the potential risk of prion diseases such as vCjD.

In all cases, Dr. Chehadeh pointed out that, as was the case with HIV and HCV, the reaction to these emerging threats has been reactive and not proactive. However, the development of a recombinant product by a method free of human and animal protein would virtually eliminate the risk of new or unknown viruses, thereby increasing protection.

With regard to the actual efficacy of the product, Dr. Chehadeh demonstrated that the factor molecule in Advate® is the same as in the 1st generation product, Recombinate®, and therefore of comparable efficacy. The new product also has a reduced volume of only 5 ml, and is available in 1500 IU vials.

As well as information on the treatment itself, data from a trial in previously treated children was also presented, and showed that no serious adverse events and no inhibitors occurred.

Finally, a presentation was given by a haemophilia nurse from the Necker-Enfants maladies haemophilia treatment centre. She provided an overview of their experience with Advate®, providing a vivid picture of the many different issues and tasks covered by a haemophilia nurse as a caregiver and a trainer.

FRIDAY AFTERNOON **LECTURES**

Registries

Beginning his presentation on the need for the establishment of patient registries, H.M. Van den Berg stated that the important data that is captured in national registries includes:

- number of patients
- factor consumption
- treatment related side effects
- patient status.

In addition, H. Van den Berg stated that registries will become increasing important as data related to cost effectiveness becomes a higher priority. Registry data could also be important for the purposes of hemovigilance and the development of care and treatment guidelines.

Having provided the background on the uses and need for patient registries, H Van den Berg went on to present an overview of a new registry, the PED-NET haemophilia registry. This is a prospective registry for patients born since 2000 and treated in one of the associated European centres. There are currently 260 patients on the registry and 90 new patients are expected each year, as well as 15-20 patients with inhibitors.

The purpose of the registry is to collect data on haemophilia patients and to improve the understanding of the pathophysiology of the disease. He noted that this will be especially valuable for understanding the causes of inhibitors, where formation is often seen within the first 75 days of exposure to factor concentrate. He then outlined that dedicated inhibitor development research is already underway where factors being tracked include gene mutation type, ethnicity, family history, breastfeeding, age at first exposure, age at start of prophylaxis, changes in treatment frequency and type of product.

She pointed out however, that a simple, but important goal of the registry, is to get an overview of the total number of patients, and it is expected, that the data on comparative treatment regimes will give important information for the future.

In a separate presentation, Angelika Bartova related the experience of the patient registry in Slovakia that was set up in the 1960's. The registry documents factors including incidence, prevalence and distribution of patients, which in turn has been used to estimate the need for treatment and blood products in the country. It is updated annually via a questionnaire, and has proven to provide an excellent overview of the situation among the Slovakian patient population.

The French experience with registries was presented by T. Lambert. He started his presentation by relating the experience of the first French registry, which was an anonymous registry for patients with haemophilia A and B. The registry recorded levels of factor use, but also included a provision whereby annual test samples were taken, stored and frozen for the purpose of future investigation, research and possible look-back examination. The registry however was seen as unsuccessful, as at best, it only covered 1,240 out of the possible 4,000 patients, and there was uneven representation between the different French regions. The sample collection element also proved to be time-consuming and no frozen samples were used for research or investigation. As a result, a new system, FranceCoag, was developed and started in January 2003. The purpose of the new system has been to collect knowledge and data on patients and to follow the patient population over time. The new registry is also anonymous, and covers all patients with coagulation defects. FranceCoag is led by a steering committee with a broad comprised of doctors, scientists and patient representatives. The steering committee is very active. Five meetings take place annually, and there have already been three publications with three more projects under way. To date, there are now 3,400 patients in the registry.

In the following workshop it was concluded, that there was no co-ordination between European haemophilia registries, and many that exist are unstructured, incomplete and under resourced. It was also noted of course, that in many countries, no registry exists at all. It was therefore agreed, haemophilia patient registries should be a requist for all countries to ensure accurate documentation of patient numbers, use of factor products and treatment needs. It was also agreed that registries should be confidential, and only anonymous data should be published. It was also considered important that in order to be able to be representative, they should cover a large part of the patient population.

SATURDAY **MORNING LECTURES**

Safety of Plasma and Recombinant Products

J.H. Trouvin gave a very clear and informative overview of the safety of plasma derived and recombinant products. He stressed that viral safety is a key element, because products derived from human or animal sources may transmit viruses of human or animal origin. He explained that reducing the risk of viral transmission includes several steps.

- Step one is to reduce the risk in the starting material by qualification of blood donors, testing of the donors and plasma pools for viruses and other starting material.
- Step two is to reduce viral load during the manufacturing processes and also include at least one step of viral inactivation during the manufacturing, with a documented ability to inactivate non-enveloped viruses by at least four logs. It was noted, that reduction is not the same as inactivation, but that both methods should be a part of the process validation.

He stressed that in all parts of the manufacturing, tests should be done at critical points and on intermediate products to give a continuous documentation of the safety of the product. Following the explanation about viral transmission risk, J. Trouvin, then went to talk about the risks associated with that of prion transmission where he mainly focused on CJD.

J. Trouvin explained that transmission has occurred during red blood cell transfusion, but no transmission with industrial plasma products has yet been seen, and that all data leads scientists to assume a very low level of infectivity. In order to minimise any risk of prion transmission, as with viruses, blood donor exclusion criteria has been introduced (so donors, who have stayed for a period of time in UK, received pituary growth hormone, cornea transplantation or neurosurgery are excluded).

J. Trouvin went on to explain that donor exclusion criteria was important because, as yet, there are no screening tests available to detect prions, and because prions are very resistant and sticky agents, there is also no known inactivation method. There are however, some production steps which can remove prions, such as leukodepletion of plasma, precipitation and chromatography, which can lower the prion load by up to three logs.

Going onto recombinant products, J Trouvin explained that they do not have the same risk of viral transmission as with plasma derived products, because the latter are derived from human blood donors which represent a constant variation, as each donation poses a new risk entering the production line.

However, with recombinant products, there is still potential risk associated with the use of cell substrates or other biological reagents like calf serum or protein fractions such as albumin which are used in the production processes, and which may contain infectious material. Therefore, he explained, the production of recombinant products are made with the same strict controls: validating and controlling all raw materials used and quality checks at all important steps during production.

J. Trouvin concluded, that the risk factors of human viruses, animal viruses and prions exist, but current experience shows that the safety of factor products are extremely high, although upcoming new viruses and still unknown transmittable agents are still a challenge in plasma derived products.

Haemophilia and Familial/Social Relationships

G. Goldstein gave a warm and passionate speech about the consequences of haemophilia on familial and social relationships. She illustrated the different stages of reactions to the diagnosis: shock, denial, anger, depression and gradual acceptance and adjustment. She emphasised that coping with a chronic illness is a lifelong process and many of the different reactions were discussed - the mothers feeling of guilt, the fathers feelings of not being able to socialize with his boy, the child's feeling of being different, not able to perform as his friends, being held outside and being the cause of many changes in the family life.

It was stressed that psychosocial support was very important for the parents and family of a newly diagnosed child, and that the opportunity to meet with others in group therapy or self-support groups was a good and successful tool to learn how to cope with the situation.

In the following discussion and workshop, it was clear, that the remarks concerning mothers and guilt triggered many reactions and comments. The way of expressing the inheritance of haemophilia as a disease "from mother to son" raised many comments, but to this feeling of guilt there was no clear answer. Many commented, that this was not so, but it also became clear, that the impact of haemophilia on the family has a lot to do with culture, religion and access to treatment. Many countries have good experience with annual meetings, summer camps, meetings dedicated to mothers only or training and education meetings, to share experience and feelings with people in the same situation. In this session it became clear, that there was a lot more to talk about…

Next Generation of Haemophilia Treaters

The next presentation about formation and education of professionals was given by Dr. Schved in the absence of J. Astermark. He introduced the presentation by illustrating that there is a declining interest in haemophilia among young doctors. With no formal specialist qualification in the field of haemophilia, thrombosis and haemostasis, he stated that there is a need for a harmonised education network between haemophilia centres.

He then presented a new haemophilia physician education initiative that took place in Malmö, Sweden in 2004. The target group was physicians with some experience in treating haemophilia patients, and the aim of the course was to facilitate early diagnosis and correct treatment of patients with haemophilia. Over one week, the course covered lectures, diagnostic tests, laboratory work discussions and literature studies. In the discussion after the presentation, concern was expressed regarding the course sponsorship from medical companies. However it was explained that the course syllabus and content was independently developed by the physicians at Malmö, and the sponsorship was purely in the form of an unrestricted grant that covered the travel expenses of some of those attending. It was discussed that ideally, education should be part of the university teaching, but it was realized, that haemostasis and thrombosis is only a small speciality in the field of medicine.

There was some agreement that haemostasis and thrombosis should be joined in at common specialist training.

It is also acknowledged, that the WFH is doing a lot of training in developing countries, and that the problem of attracting new doctors in developed countries is partly a result of successful treatment, giving fewer challenges to those who treat patients.

In a conclusion, the idea of having at formalized course in haemophilia was accepted, but it was proposed, that this should be supported by national health authorities as a specialist education, and that these courses should be developed by a medical advisory board or by courtesy of a medical society.

EU Regulatory Enviroment for Haemophilia Products

R. Seitz gave an overview of the European regulatory environment for haemophilia products. He stated that there are different levels of regulations based on national, EU, Council of Europe or international agreements. A key institution is the EMEA (the European Medicines Agency) **http://www.emea.eu.int/,** which evaluates and grants marketing authorization of medical products in the EU. This evaluation can be done via a single evaluation carried out through the Committee for Medicinal Products for Human Use (CHMP), through decentralized mutual recognition or in a single country only.

Industry Overview

C. Waller from the Plasma Protein Therapeutics Association (PPTA) gave an overview of the current status of the European Industry.

He began his presentation by focusing on the challenge of vCjD transmission in Europe. He stated that so far 155 cases have been seen in the UK, one in Ireland, one in USA and one in Canada (all UK linked). There have then also been 11 cases in France, and ones in Italy, the Netherlands and Japan, which could not be related to UK, with cases occurring in other countries which cannot be excluded.

As a precaution against vCjD, C. Waller explained that plasma from the UK is not used for fractionation, and donor exclusion criteria have been established all over Europe. Although two cases of transmission of vCjD have been published, it should be understood that these transmissions were not through plasma products. Units of plasma are diluted, and during processing the agent is reduced.

C. Waller also raised the issue of inhibitor formation in haemophilia treatments. He stated that inhibitor formation was not clearly understood and there is perhaps a need for greater study of inhibitor appearance data and the conduction of post marketing studies.

Theo Evers and C. Waller then gave an overview regarding improvements to product information, which is an important goal for EPFA (now IPFA). The goal is to improve transparency, product information, pharmacovigilance and interaction with patients and authorities. Part of the initiative will be to have much closer involvement of patient associations regarding the drafting of package inserts and information, as well as guidelines and risk/benefit information. Pharmacovigilance and patient education programmes are also being considered.

The next issue covered was that of product supply. C Waller stated that this is now considered sustainable, with enough clotting factor to meet clinical need in Europe.

Difficulties however are arising due to increasing regulatory and technical demands, as well as the overall pressure of healthcare funding.

With regards to purchasing, the many different ways of purchasing were discussed, including regional or central systems, and by tenders or contracts. The pros and cons for these different ways were discussed.

Haemophilia in the EU – Threats & Opportunities

B. O´Mahony gave us all something to think about in his speech on threats and opportunities for haemophiliacs in tomorrows Europe.

Data was presented from the last WFH Global Survey, which demonstrated the wide variations between countries in diagnosis rates and treatment levels. It was also clear that the treatment levels and factor consumption rates were unknown in many countries. Data on factor usage compared to population revealed large differences between European countries, with only four countries using above four units per capita, and 11 countries using under one unit per capita. With an expanding Europe, the average use has changed from 1.9 units to only 2.2 units over a ten year period, a key reason being the low proportion of GDP spent on health in some of the new EU Member States.

B. Mahony then also pointed to future threats to haemophilia care in Europe, citing government retrenchment, the demand for more evidence based medicine and the tendency to compare treatment costs between therapy areas as key challenges.

One threat that is already being seen is the survival of HTCs, which can be viewed by healthcare providers as non-cost effective given the small patient population size they serve. A possible solution suggested to ensure the survival of a threatened HTC, is to widen the scope of the HTCs remit, and join with thrombosis and haemostasis. The number of patients served would rise, and the cost per patient would lower – thereby making an HTC more viable.

B. O'Mahony then illustrated a current risk to haemophilia care by citing a recent case in New Zealand, where the cost of treating a boy with haemophilia became a media issue. The media positioned the story that the cost of treating this boy meant denial of treatment for patients with another diseases. Lessons regarding media handling, humanisation of the story and aggressive lobbying were learnt.

B. O'Mahony then also stressed the importance of registries, the need for evidence of the benefits of prophylaxis and data that demonstrates the hidden cost of providing unsafe treatment.

A clear message was to humanise contact with authorities, focus on average costs, outline the benefits of treatment and be proactive and be heard in the development of new directives, policies concerning health policy issues.

EHC General Assembly Meeting

Dr. Hubert Hartl, the EHC Chairman, presented an outline of a new EHC initiative to raise awareness of haemophilia among EU health policy makers. The aims of this project are to:

- Build and maintain political focus on haemophilia
- Enlist key policy makers and key opinion leaders to champion the needs of people with haemophilia and their families
- Sensitise the public to the specific needs and concerns of PWH and their families across Europe
- Promote the concept of enhanced cooperation between PWH, the medical profession, and health policy makers
- Protect the future of haemophilia care and ensure PWH have access to the best level of care provision and safest treatments

He stated that the project had the following phases:

- A haemophilia survey among EU policy makers with resultant report (May/June 2005)
- A European Parliament event to which NMO representatives would be invited (Autumn 2005)
- The development of a set of national haemophilia information fact sheets, developed in cooperation with NMOs and translated into local language

Sunday Morning Lectures

M. Anderson, from the Swedish society, gave a short presentation on the Arosenius foundation and invited participation at the next meeting to be held in Sct. Petersburg. Main topics will be optimization of pro phylactic treatment and orthopaedic treatment.

The Belgian Society presented a very interesting project for an educational CD-Rom. Based on experiences from summer camps, it was realised, that there was a possibility to take advantage of IT and create an interactive CD that could be attractive to youngsters.

The concept is an interactive comic strip (which Belgium are so world famous for), with a story about a young boy with haemophilia. In the story, different problems have to be solved in an interactive way. The concept is to educate and impart information through playing games in a way that is understandable for the target group, without moralising or focusing on the word haemophilia.

The project is not finished yet, but the preliminary demonstration was very impressive and the audience reaction very positive. The game will be translatable, and it will be possible to obtain the CD later. It is a very new and exciting project that we will all follow with great interest.

At the end of the meeting, both the president of the French Haemophilia Society, Edmond-Luc Henry, and the chairman of EHC, Hubert H. Hartl, thanked speakers and organisers as well as sponsors for a very well organized and successful meeting.

In Conclusion

Many different topics were discussed at this year's very successful meeting.

We have reached a very high level of treatment safety, but are facing a climate of healthcare budget scrutiny, that caused some to question whether the community is facing a choice between access to safer treatment, or access to more treatment.

Discussion on sports focused not on the question of whether it should be encouraged, but rather, the level of risk involved in more active sports. It gave me a picture of the improvements over the last thirty years, because when I was young, any kind of sport was strictly forbidden!

The psychosocial aspects of haemophilia provoked a lot of comment and discussion, particularly regarding a mother's feelings of guilt. The intense reaction to this issue indicated that this was a topic of great interest and thus more time for discussion is needed to, quote, "repair broken wings of angels". It is an important task for NMO´s to be aware of the problems faced by families with newly diagnosed haemophiliacs and to facilitate contact persons and self support groups.

Future challenges are the increasing focus on the cost of haemophilia treatment, the cost of increasing safety and the competition among other patient groups and emerging treatments when the health budget is limited. It is more important than ever, to have good registries to document the need for treatment and to prove that safe and adequate factor supply, is the key to good quality of life.

EDITORIAL BOARD

steering comitee of the EHC
European Haemophilia Consortium
Österreichische Hämophilie Gesellschaft (ÖHG)
SHZ im AidsHilfeHaus
A-1060 Vienna, Mariahilfer Gürtel 4
Österreich
E-Mail: ehc@bluter.at

authors of this issue:
Theis Bacher

The minutes of the general assembly meeting will be published separately.