

European Association for Haemophilia and Allied Disorders



1st Annual Congress

14th & 15th February 2008

The De Groote Industrieele Club

Dam 27

Amsterdam

**European Association of Haemophilia & Allied Disorders
1st Congress
Amsterdam**

Thursday 14th February

9.30	Registration and coffee	
11.00	Introduction Dr Hubert K. Hartl – an appreciation European Association for Haemophilia and Allied Disorders – a progress report.	C.A.Ludlam J. Ingerslev
11.30	European Haemophilia Safety Surveillance Project (EUHASS) Background Practical plans and arrangements	P. M. Mannucci M. Makris
13.00	Lunch	
14.00	Clinical Practice Symposium Chairs B.T.Colvin and W Schramm	
	<ul style="list-style-type: none">▪ Problems with FVIII:C assessment▪ How do I measure vWF?▪ DDAVP – when and how it should be used	M. Makris P. Lenting G. Castaman
15.30	Tea	
	<ul style="list-style-type: none">▪ How do I manage surgery in VWD?▪ How do I manage surgery in haemophilia?	S. Lethagen K. Peerlinck
17.00	Boat Tour of Amsterdam (pre-booked places only)	
19.45	Pre-dinner drinks	
20.30	Informal Dinner	

European Association of Haemophilia & Allied Disorders 1st Congress Amsterdam

Friday 15th February

09.00 Presentations by European Research Groups

Chairs C.A.Ludlam and P.M.Mannucci

- Introduction C.A Ludlam
- EAHAD Nurses Committee H.Thykjaer
- PedNet R. Ljung
- Rare Disorders Registry J. Goudemand
- HIV exposed but uninfected individuals with Haemophilia A. McMichael
K. Shianna

10.30 Coffee

- Study of immunological markers in patients undergoing ITI (ObsITI) W. Kreuz
- Von Willebrand Disease Prophylaxis Network E Berntorp
- Alloantibodies in type 3 VWD A.B. Federici
- Review of EAHAD meeting C.A.Ludlam

12.00 Lunch

13.00 Symposium

Chairs H.M. van den Berg and H. Thykjaer

- Prophylaxis for Haemophilia K Fischer
- Anti-factor VIII inhibitors arising in childhood – what's new? E A Chalmers
- Inhibitors in haemophilia B - an intriguing complication J Ingerslev

14.30 Tea

- New products with enhanced efficacy for treating haemophilia C Negrier
- Health status in older persons with haemophilia and how they manage their condition S von MacKensen

16.00 Close

European Association for Haemophilia and Allied Disorders

Executive Committee

Professor Christopher A Ludlam	President
Professor Pier M Mannucci	Vice-president
Professor Jørgen Ingerslev	Secretary
Professor Jan Astermark	Treasurer
Dr Brian T Colvin	Company Secretary
Professor Claude Negrier	
Professor Ian R Peake	
Professor Wolfgang Schramm	
Ms Hanne Thykjær	
Dr Marijke van den Berg	

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Financial assistance is gratefully acknowledged from

Baxter BioScience

Bayer HealthCare

CSL Behring

Kedrion

Novo Nordisk

Octapharma

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Wyeth

Abstracts

European Haemophilia Safety Surveillance Project (EUHASS)

Mannucci PM and Makris M,

Universities of Milan and Sheffield

Although medicines have to be shown to be safe in clinical trials before they are licensed, these trials usually involve very few highly selected patients. Long term pharmacovigilance is essential for all medicinal products. This is poorly done since clinicians fail to report events to regulatory authorities because they are busy, believe the adverse event is well known or wish to wait and report their own series first.

EUHASS is a large, multicentre, prospective surveillance project that will be run in Europe for 3 years starting in 2008. Initially it will be in English only and will be entirely electronic. 45 haemophilia centres from 26 European countries have agreed to take part. All haemophilia and von Willebrand's disease patients in these centres will form the basis of the prospective surveillance. In total 14,522 patients will be followed up and these include >5000 patients with severe haemophilia A, >800 with severe haemophilia B and >300 with type 3 VWD. At the start of the study all centres will provide cumulative data on how many patients are registered with them and how many were treated with clotting factor concentrates in the previous 12 months. Once the surveillance starts centres will get an email every 3 months asking them if they have had any patients developing a new inhibitor, thrombosis, transfusion transmitted infection, allergic reaction, new malignancy, new cardiovascular event or death in their patients. Centres responding positively will then be asked to fill in some more very basic information about the events. All events will be reported anonymously. Every 12 months centres will report cumulatively on how many patients in their centres received each concentrate.

One of the key areas of interest will be inhibitor development. All products used to treat patients with haemophilia will be prospectively surveyed and this will include recombinant as well as plasma derived products. Annual the number of previously untreated patients, minimally treated patients and patients with have switched products in the previous year will be reported.

The IT support for the study will be provided by the UKHCDO Ltd in Manchester in the UK. The other associate partners are the University of Utrecht who will perform all the analyses and produce all the reports, the University of Milan who will maintain a concentrate registry

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and the European Haemophilia Consortium which will develop a registry of all haemophilia centres in Europe and help set up a rapid response system. The project is funded by a grant from the European Union (60%) as well as support from the pharmaceutical industry (40%).

Further information can be obtained from: m.makris@sheffield.ac.u

Problems with FVIII:C assessment

Mike Makris,

University of Sheffield, UK

The methodology for FVIII:C assessment has been in regular use for the management of haemophiliacs for more than half a century. Despite this, problems in its performance and interpretation continue. The commonest method used internationally is the one stage assay which is preferred due to its simplicity, ease of automation and cost. The other two methods i.e. the chromogenic and two stage clotting assays are much less frequently used.

This lecture will discuss some of the issues with the FVIII:C estimation including

a) The quality control of the assay

External quality control is essential in ensuring the ongoing accuracy of a laboratory's FVIII assay. In every external quality assessment exercise there is invariably a bell shaped curve of results with a range of values for the same sample.

b) The normal range

It is important for each laboratory to construct their own normal range for the reagents and instrument combination that they use. The often quoted normal range of 50-150% is inaccurate and biologically implausible.

c) The use of these assays to measure very low factor VIII levels

The ISTH definition for severe haemophilia stipulates a FVIII:C level of <1% but it is often difficult to generate accurate results that will differentiate from example a 0.5% from an 1.5% patient.

d) The problems of patients with mild haemophilia and discrepant FVIII:C levels

When FVIII:C of mild haemophiliacs is measured by both the one-stage and two-stage/chromogenic assay around 30% of patients have discrepant levels. In most cases this is not clinically important because patients would be treated with desmopressin in any case.

This discrepancy is however important in two groups of patients, firstly those with reduced two-stage but normal one-stage assay where the diagnosis of haemophilia will be missed and

secondly patients with low one-stage but normal two stage assay where the “incorrect” diagnosis of haemophilia is made.

e) The problem with measurement of high FVIII

Increasingly laboratories measure high FVIII levels for use in the estimation of thrombotic risk. It is often not appreciated that the CV of the assay when measuring high levels is 10-20% nor that the high risk is continuous and not dichotomous. The precise risk associated with each level is often unclear.

How do I measure von Willebrand factor?

P.J. Lenting

Van Creveldkliniek, University Medical Centre, Utrecht, The Netherlands

Von Willebrand factor (VWF) is a complex glycosylated protein that contributes to a number of physiological processes. Mutations in the gene encoding VWF may result in a (partial) deficiency or dysfunction of the protein, associated with the bleeding disorder von Willebrand disease. The recognition of defects in VWF protein levels or function is obligatory for optimal treatment of patients suffering from this disorder.

Due to the multi-functionality and the complexity of VWF, a number of laboratory assays are available to investigate the various aspects of VWF structure and function. These include basic assays such as platelet-count, VWF antigen, ristocetin-cofactor activity, RIPA and collagen-binding, but also more advanced assays such as multimer analysis using SDS-agarose electrophoresis and factor VIII-binding. Although most of these assays are in use for 10-20 years, the improvement of these assays is a continuous process.

In recent years, a number of new assays have been developed, including the platelet-function analyzer (an in vitro approach mimicking the bleeding time-test), assays to measure VWF-propeptide and assays to measure the amount of VWF that is in its active conformation.

The presentation will focus on the various aspects of measuring VWF in relation to its structure, function and clinical relevance.

DDAVP- When and how it should be used

Giancarlo Castaman

Department of Hematology and Hemophilia and Thrombosis Center, San Bortolo Hospital, 36100 Vicenza, Italy

Following its first clinical use in 1977, desmopressin has rapidly emerged as the treatment of choice for patients with mild hemophilia A (Factor VIII coagulant activity, FVIII:C > 5 %) and von Willebrand disease type 1 (1). In these patients usually FVIII:C is increased 2 to 6 folds by the compound. Desmopressin is cheap, safe and carries no risk of transmitting viral infections. The widespread use of the compound in clinical practice has spared several patients the risk of acquiring blood-borne viral infections particularly during the HIV outbreak prior to 1985 (2). In Italy, where the compound has been largely used since the end of 70s, desmopressin has reduced the number of HIV infections in patients with mild hemophilia A approximately by at least 8-fold compared to USA hemophilia A patients (2). During the 80s, the avoidance of the risk of blood-borne infections was the main advantage perceived. Despite the fact that safer plasma virally-inactivated and recombinant FVIII/VWF concentrates are now largely available, the costs of this treatment still favour the use of desmopressin. Furthermore, the compound avoids the potential occurrence of inhibitors in those mild hemophilia A patients at risk upon treatment with FVIII concentrates (especially those with Arg593Cys, Trp2229Cys and Tyr2105Cys mutations)(3). In this setting, DDAVP can be used in association, especially during surgery, to lessen the amount of FVIII infused, a strong predictor of inhibitor appearance in these patients (3). However, FVIII and VWF concentrates remain the mainstay of treatment for the patients in whom desmopressin is contraindicated or is not able to induce an adequate increase of FVIII levels.

While the correction of low FVIII level is the only aim of treatment in hemophilia A, in patients with VWD the abnormal platelet-vessel wall interaction and platelet cohesion must also be corrected by raising VWF levels. We still do not know if a genetic background could be responsible for the variability of responses in hemophiliacs with similar FVIII:C at baseline. On the other hand, patients with VWD showing significant basal multimeric abnormalities, mostly caused by mutations in D3 and A1-A3 domains of VWF subunit (some type 1 and most type 2 A and B VWD), usually display poor biologic responses to desmopressin (4,5). However, since the relative high consistency of responses to separate

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infusions (6), a test with the compound is advised prior to its clinical use, especially in pediatric hemophilic population which is at greater risk of poor response (7).

Although several reported series of treated patients have clearly demonstrated the efficacy and safety of desmopressin in the treatment or prevention of bleeding episodes in hemophilia A and VWD, no controlled studies have been carried out to clarify which minimal FVIII:C threshold post-infusion is required to achieve clinical efficacy. It is generally believed that a level post-infusion of at least 30 U/dL should suffice for the treatment of minor bleedings or for minor surgery (8). On the other hand, a level > 50 U/dL post-administration is required for treatment of major surgery. However, in the latter case, since several administrations over a short period of time are anticipated to maintain adequate through FVIII:C levels, the clinical efficacy of the compound could be hampered by tachyphylaxis (9).

Typically, acute bleeding episodes in both the disorders are best managed by intravenous desmopressin since the raise of FVIII and VWF is more rapid than with subcutaneous injection, even though the magnitude of response is similar. Subcutaneous (and, if available, intranasal) route is to be preferred for home-therapy (10).

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How I manage surgery in von Willebrand disease ?

Stefan Lethagen

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Summary

Patients with von Willebrand disease (VWD) have an increased bleeding tendency in connection with surgery or other invasive procedures. It is generally agreed that the low von Willebrand factor (VWF) level is most important for mucous membrane bleeds, whereas decreased factor VIII (FVIII) is more important for soft tissue bleeds¹⁻³. VWF levels should be normalized perioperatively and in the early postoperative period, especially when there is a risk for mucous membrane bleeds. FVIII should be normalized in connection with major surgery, both during the surgical procedure and for about 7-10 days postoperatively⁴.

Factor levels can be raised either by stimulating the endogenous release of FVIII and VWF with desmopressin (DDAVP, 1-desamino-8-D arginine vasopressin), or by substituting the deficient factors with a coagulation factor concentrate containing VWF and FVIII.

DDAVP

DDAVP is a widely used hemostatic drug which increases FVIII, VWF and also tissue plasminogen activator, usually with 2-6-fold, through endogenous release^{5, 6}. Most patients with type 1 respond adequately to DDAVP, whereas most type 2 patients will have an insufficient response due to functional abnormalities in the VWF. In the classical form of type 2B, DDAVP cause platelet aggregation and thrombocytopenia, and should not be used^{7, 8}. Type 3 patients do not respond to DDAVP. All patients should be given a test dose to ensure that the response is sufficient for clinical use. DDAVP can be used for treatment of major bleeds, or for prevention of bleeding in connection with surgery or other invasive procedures, if VWF:RCo and FVIII:C reach normal levels after DDAVP.

In case of surgery, DDAVP (0.3 microgram/kg) may be given intravenously (i.v.) about 30-60 minutes before surgery, or subcutaneously (s.c.) about 1-2 hours before surgery. The intranasal spray may be used in connection with minor procedures, and should be taken 1-2

hours in advance in a dose of 300 microgram (150 microgram in patients weighing less than 30 kg)^{9,10}.

The DDAVP dose can be repeated at 8-12 hour intervals if necessary. If repeated dosing of DDAVP over several days is required, anaphylaxis and antidiuretic effects must be considered. It may be necessary to switch over to a factor concentrate in some cases. A single dose of DDAVP is often sufficient for minor surgery. In connection with tooth extractions and other procedures involving mucous membranes, it is advantageous to give an antifibrinolytic agent, e.g. tranexamic acid, concomitantly.

Factor concentrate

Patients who are unresponsive to DDAVP, i.e. severe type 1 patients, the majority of those with type 2, and all type 3 patients, require concentrates containing large amounts of VWF in case of bleeds or surgery. Some type 1 patients may also require VWF concentrates if they need prolonged treatment, or if they have contraindications to DDAVP, such as cardiovascular disease.

Several VWF concentrates are available; most of them also contain FVIII. There may be considerable differences in the relative concentration of VWF and FVIII and of the functional activity of VWF^{11, 12}.

The dosing of a concentrate is dependent on the patients' own basal level, and the nature and severity of the bleed or the procedure. A recent prospective study of one of the most used VWF/FVIII concentrates, showed that a pre-operative pharmacokinetic (PK) investigation was useful for determining the loading dose applied for surgery¹³. Successful hemostasis was attained with a median VWF:RCo loading dose of 62.4 IU kg⁻¹ (inter-quartile range 50.1–87.0) in subjects with various types of VWD undergoing minor and major surgery. The median in vivo recovery of VWF:RCo was 1.9 IU·dL⁻¹·(IU·kg⁻¹)⁻¹ after the loading dose. Median half-life was 15.6 h (IQR, 9.0–28.4 h). Postoperative mean trough VWF:RCo levels of 62–73 IU dL⁻¹ were sufficient to prevent bleeding¹³.

VWF concentrate administration is usually repeated every 12-24 hours post-operatively. A VWF concentrate can also be administered as a continuous infusion. Levels of VWF:RCo

and FVIII:C should be monitored when treatment is protracted. Long-lasting FVIII:C levels above 1.5-2 kIU/mL should be avoided due to a risk of thrombosis.

Antifibrinolytic agents

Tranexamic acid is probably the most widely used antifibrinolytic agent in VWD. More adverse effects hamper the alternative antifibrinolytic, epsilon-aminocaproic acid. Tranexamic acid can be used alone for minor procedures, or in combination with DDAVP or a VWF factor concentrate, when mucous membranes are involved.

Summary

Surgical procedures can safely be performed in patients with VWD given sufficient hemostatic treatment. DDAVP can be used for selected responders. When choosing a VWF concentrate, the relative content of FVIII and VWF, and the functional capacity of the VWF must be considered. A pharmacokinetic test may be supportive for tailoring the pre-operative loading dose of a VWF concentrate.

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PEDNET (European Paediatric Network for Haemophilia Management)

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Since 1997, paediatricians from haemophilia centres in 16 western European countries have shared their experience through annual informal meetings, within the European Paediatric Network for Haemophilia Management (PedNet). The annual workshops, with invited lectures by experts on specific topics, serve as a forum for informal discussions on clinical practice and research with the aim to improve quality of care of children with haemophilia. Furthermore, the network provides an infrastructure for clinical research. In 1998, a survey was done that provided a snap-shot of the care of boys with haemophilia in Western Europe. This report demonstrated significant discrepancy between centres, particularly with regard to treatment schedules. This survey was updated in 2003 and showed that regular, continuous long-term prophylaxis was provided in all PedNet centres, with 80–100% of boys being treated this way in most of the centres. Twenty of the 22 centres (91%) recommended continuous prophylaxis (primary or secondary A) for a new patient. The PedNet members have also discussed and suggested definitions (i.e. glossary) on prophylaxis, target joints, re-bleed etc that have been communicated by Meeting Reports in ‘Haemophilia’ and widely accepted and used in the haemophilia community. Several PedNet centres participated in the development of the ‘European MRI score’, the first additive MRI score of haemophilia arthropathy with the ability to distinguish reversible and irreversible changes in the joint. Other centres have participated in the refinement of a new orthopaedic score suitable for children. The PedNet Registry was started in 2004 with the aim to provide a collection of basic data on all children born after January 1,2000, in the participating PedNet centres. About 90 children per year will be added to the Registry, which today has around 400 entries from 21 participating centres. The database will be used for various studies, the first being the on-going RODIN-study on risk factors for development of inhibitors during the first 75-exposure days. Several other studies using the Registry are currently being discussed. Several papers and meeting reports have been published ‘on behalf of PedNet’. The PedNet has been sponsored by Bayer.

Rare Disorders Registry

Jenny Goudemand on behalf the European Network on Rare Bleeding Disorders (EN-RBD).

Rare bleeding disorders (Fibrinogen, FII, FV, FV+FVIII, FVII, FX, FXI and FXIII deficiencies) are rare hemorrhagic diseases with prevalence in the general population varying between 1 :500 000 and 1 :1 000 000. The clinical expression is variable. In order to improve the knowledge of these diseases an international registry was created in 2005 (www.rbdd.org). About 400 patients from 19 countries are already included in this registry. However it appeared that collection and organization of clinical, laboratory, treatment data and their statistical analysis using a unique and homogenous model was necessary to indicate which course of action is really needed to improve diagnosis and treatment of these diseases. In this frame a European network project was prepared and funded by PHEA (Public health Executive Agency) in 2006. Each of the 10 participating centres (from Italy, Denmark, France, Germany, Greece, Ireland, Slovenia, Turkey, UK) will insert and manage patients' data through a protected access area on the www.rbdd.eu web site following the same data collection scheme. Beside the development of a network of European centres dealing with patients affected by RBDs, the main goals were to standardize laboratory methods for phenotype and genotyping analysis and to verify the possibility to merge already National Registries in a unique, homogenous data base that could help to develop epidemiological data and exchange the best medical practice. The final goal will be to make the network accessible to all centres in Europe and spread worldwide once it will be established and correct correctly operating.

Investigation of gene variation associated with resistance to HIV-1 infection in HIV-1 exposed but uninfected individuals with haemophilia A

Andrew McMichael*, Lucy Dorrell*, Kevin Shianna[†], David Goldstein[†], Barton Haynes on behalf of CHAVI

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The Center for HIV/AIDS Vaccine Immunology (CHAVI, www.chavi.org) is one of two implementation projects under the Global HIV Vaccine Enterprise that will develop new vaccine strategies to overcome key immunological roadblocks in HIV vaccine design. These roadblocks include a lack of understanding of the correlates of protective immunity to HIV-1. At the beginning of the HIV-1 epidemic, use of clotting factor concentrates which had not been subjected to viral inactivation procedures led to the tragic consequences of HIV-1 (and hepatitis C virus) infections in the majority of exposed haemophiliac subjects. However, a significant minority were not infected with HIV-1 despite a high probability of exposure. Up to 25% of the uninfected individuals are homozygous for the CCR5 Δ 32 allele and thus have almost complete resistance to infection by HIV-1. By contrast, homozygosity for this allele is \leq 1% in the general population, demonstrating the importance of genotype in resistance to HIV-1 infection, but explaining only a small proportion of these cases. In order to identify other genetic polymorphisms that influence susceptibility or resistance to HIV-1 infection, CHAVI is conducting a whole genome association study in HIV-1-exposed but uninfected individuals with moderate or severe haemophilia A who received infusions of FVIII concentrate during 1979-84. DNA samples from between 400-1000 haemophiliac subjects will be analysed using Illumina human genotyping beadchip which can detect over 500,000 single nucleotide polymorphisms. The results will be compared with an existing cohort of HIV-1-positive controls. CHAVI wishes to invite Haemophilia Treatment Centres across the world to contribute peripheral blood or DNA specimens from their existing cohorts for this analysis. Data mining and specimen submission costs will be reimbursed at a pre-arranged sum and collaborators will be coauthors of any publication. The full genetic information

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gained will be made available to all participants. The information generated will be used by CHAVI to identify new targets for HIV-1 vaccine design. CHAVI has leading experience in whole genome association studies in HIV-1 infection, having previously worked with European scientists to identify new genes associated with control of HIV infected people (Fellay et al., Science 2007; 317: 944).

An observational research program (ObsITI) on immune tolerance induction in patients with haemophilia A and F VIII inhibitors

Wolfhart Kreuz, Carmen Escuriola Ettingshausen, Christoph Königs, Sebastien Lacroix-Desmazes, Srinivas Kaveri, Jan Astermark, Erik Berntorp

The development of inhibitors occurs in around 25% of severe haemophilia A patients and is therefore a serious complication of factor (F) VIII replacement therapy. Immune tolerance induction (ITI) is a powerful tool to eliminate inhibitors.

Success rates of ITI may vary depending on patient variables (e.g. inhibitor titres at start and during ITI) and on factors related to the therapeutic regimen. During the last years the product chosen for ITI, particularly the content of von-Willebrand-Factor (VWF) is highly discussed.

Therefore a research program was created in order to evaluate success of ITI according to the Bonn protocol in 200 severely or moderately affected haemophilia A patients with newly developed or already existing F VIII-inhibitors. 100 patients will be recruited retrospectively and 100 prospectively.

Primary endpoint is success of ITI (complete, partial success; partial response; failure).

Secondary endpoints are the evaluation of the impact of product type (content of VWF), the clinical relevance of individual in vitro testing (variation of inhibitory reactivity and haemostatic role of variation of inhibitory reactivity with different F VIII concentrates) and product selection, time necessary to achieve ITI, impact of inhibitor titres before and during ITI, maintenance of ITI and possibly ITI efficacy related events during ITI treatment phase. For individual in vitro testing patient plasma is tested against different types of F VIII concentrates and inhibitory activity is measured according to a modified Oxford method and by measuring thrombin generation. Epitope mapping (before and during ITI) is also performed and will be correlated with the course and outcome of therapy.

Course of ITI, including frequency and dosage of FVIII, inhibitor titre at start of ITI, peak titre, interruption of ITI, surgeries, severe bleedings, concomitant medications/concurrent diseases and previous treatment approaches are document and evaluated.

A sub-study on immunological markers in the prospective patient group will be started soon. The following immune markers will be studied: different subpopulations of circulating T-

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cells; number, maturation state and endocytosing capacity of different antigen-presenting cells (circulating monocytes/macrophages, dendritic cells and B cells); identity of circulating cells that have endocytosed F VIII; F VIII-specific B-cells; inflammatory potential of the patients' plasma.

As of June 2007, 71 inhibitor patients from 6 countries have been recruited. Documentation has been completed in 25 cases and evaluated according to the above mentioned criteria.

VON WILLEBRAND DISEASE PROPHYLAXIS NETWORK

Erik Berntorp,

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Results from cohort and registry studies confirm that a subset of people with VWD experience a significant degree of morbidity from mucosal bleeding, e.g., epistaxis, gastrointestinal bleeding, and menorrhagia, and also from joint bleeding [1]. Studies conducted in Sweden have shown dramatic decreases in bleeding frequency following onset of treatment of prophylaxis [2]. Notably, subjects who began prophylaxis at an early age because of mucosal bleeds never developed joint problems later in life [3].

The VWD Prophylaxis Network (vWD PN) is an international study group formed with the goal of investigating the role of prophylaxis in clinically severe VWD[4]. A survey conducted in 74 centers by the vWD PN showed that of 6208 people cared for, 102 (74.5% type 3, 17.6% type 2, and 7.8% type 1) were under treatment with prophylaxis. The most frequently cited reasons for initiating prophylaxis were joint (40%), epistaxis/oral (23%) and GI bleeding (14%), and menorrhagia (5%). Based on these findings, the vWD PN initiated the VWD International Prophylaxis (VIP) Study, with the goal of establishing optimal treatment regimens for the most common bleeding indications through prospective and retrospective data collection.

In the prospective study, participants will undergo an escalation from one to three dose levels of VWD product, based on responsiveness to treatment, similar to the design of the Canadian prophylaxis trial in hemophilia [5]. The retrospective studies will examination of the effect of prophylaxis on bleeding frequency and the natural history of GI bleeding.

We believe that this comprehensive study will identify and implement optimal prophylaxis regimens for VWD, especially among those with type 3, who are the most severely affected by the disease.

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Project: Prevalence, molecular-clinical markers for diagnosis and management of alloantibodies in von Willebrand disease type 3 (PMCMDM-AlloVWD3)

A B Federici and L Baronciani

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Background: Alloantibodies against von Willebrand factor (VWF) are a rare complication of replacement therapy (7.5-9.5% of the 150 cases tested) in transfused patients with inherited type 3 von Willebrand's disease (VWD) and are mainly related to deletions of the VWF gene. In these cases, VWF concentrates not only are ineffective, but may even cause post-infusion life-threatening anaphylaxis, due to the formation of immune complexes. Attempts to manage these patients have been made by using recombinant FVIII (rFVIII) in continuous intravenous infusion at very large doses to keep FVIII levels always above 50 U/dL, or by recombinant activated factor VII (rFVIIa) to by-pass the action of such inhibitors. Due to the relatively low frequency of VWD type 3, the costs and difficulties of its molecular diagnosis and identification of antibodies, the current world-wide incidence, clinical-molecular diagnosis and management of this rare complication are not available.

Objectives: The main objectives of this investigator-driven project are: 1st step) to determine the actual prevalence and the clinical-molecular markers of the patients with alloantibodies to VWF among a very large population (at least 500 cases) of inherited VWD type 3 enrolled in this survey in both developed and developing countries (**international registry on VWD type 3**); 2nd step) To standardize methods to test alloantibodies and molecular gene deletions. **Organization of the project:** The project will be coordinated by the Clinical and Laboratory Unit on VWD of the Angelo Bianchi Bonomi Hemophilia Thrombosis Center, University of Milan (coordinator) in collaboration with at least 15 Hemophilia Centers world-wide. Clinical information from a large network of Hemophilia Centers worldwide (Canada, Europe, India, Iran, Japan, South America, USA), all expert in

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VWD management will be collected by using a specific questionnaire on line, with bleeding history measured by the bleeding severity score (BSS) recently validated in European families with VWD type 1. Values of the BSS will be related to the VWF phenotype and with FVIII levels. The first level test for alloantibodies will be performed locally according to standard protocols provided by the Steering Committee of the project. Plasma and DNA samples of individuals suspected (already transfused) or at risk (still untreated) will be centralized to expert labs for a better characterization of alloantibodies and for the identification of VWF gene defects. The titer of allo-antibodies will be measured against all VWF activities. Southern blots analysis and/or sequencing of the whole VWF genes will be used to search for deletions and mutations. Detailed information on the methods to be used for the collection of the clinical and laboratory parameters will be available on web-site within March 2008.

Prophylaxis for severe haemophilia: where do we stand and what answers do we need?

Kathelijn Fischer

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Extensive data from observational studies and a recent RCT have established that early prophylactic treatment prevents bleeds and arthropathy in boys with severe haemophilia. Over the last decades, an enormous improvement in outcome and quality of life has been achieved for our patients. However, the search for the optimum and most efficient treatment regimen is ongoing and many of the key questions are only partly answered.

The first question is when to start prophylaxis. The key is to start early; however, this is hampered by issues of venous access. Some state that prophylaxis should be started before the age of two years, others advocate consideration of the patients' bleeding pattern.

The second question is: which is the optimum treatment regimen? If cost was not an issue, using high very doses would probably be standard. The key issue is whether certain trough levels should be maintained to prevent bleeds; how strong is the association of time below 1% FVIII activity and bleeding frequency?.

And if we choose a prophylactic regimen, should we always give 25-40 IU/kg at least three times per week? What is the efficacy of low frequency regimens targeted at activities? Could we start with prophylaxis once weekly in our young patients?

The third question is if we can consider tapering or discontinuing prophylaxis in some of our adult patients. Two issues are very important here: are adult joints really less susceptible to the destructive effects of bleeds? And how to select the patients with the milder bleeding phenotype that may be candidates for switching to less intensive treatment.

Collaborative research efforts are needed to answer these questions. The challenge is to achieve adequate patient numbers as well as adequate follow-up, as severe haemophilia is a very rare disease, and functional impairment due to (repeated) joint bleeds take several decades to become clinically apparent. RCTs are costly, resulting in a limitation of both patient numbers and length of follow up.

Observational studies tend to be more generalizable and cheaper, as they use treatment protocols in agreement with routine care, and use available data. Therefore, observational studies can be much larger and of longer duration than RCTs; and are the preferred design for the evaluation of long term treatment effects. The EAHAD may provide an excellent base for these studies.

Anti-FVIII inhibitors arising in childhood – what's new ?

E. A. Chalmers

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In the developed world inhibitor development is now the most important complication of haemophilia treatment. As well as limiting treatment options and resulting in significant morbidity, the management of this complication is a substantial economic burden.

There is currently considerable interest in trying to predict which children with haemophilia will go on to develop inhibitors and research has focused on trying to identify both predictive and potentially protective factors.

The following genetic and environmental variables have been identified as potentially influencing inhibitor development in children with haemophilia and will be reviewed in this presentation.

Genetic Variables:

- FVIII molecular defect
- Family history of inhibitor development
- Ethnicity
- Polymorphisms in immune response genes

Environmental Variables:

- Age at first treatment
- Early treatment intensity
- Choice of product
- Concomitant immune system challenges e.g. Infection
- Prophylaxis

Inhibitors in haemophilia B - an intriguing complication.

J. Ingerslev.

Inhibitor formation in patients suffering from classical haemophilia represents a major complication. While significant progress has been achieved in epidemiology and practical management of inhibitors occurring in haemophilia A, the picture in haemophilia B is less clear and differs significantly from that observed in haemophilia A. We generally anticipate a risk of inhibitors in haemophilia A patients with the severest phenotype to be around 30%, and major risk is conferred in those patients who suffer from a gene mutation that completely abolishes synthesis of factor VIII. In comparison, the incidence of inhibitors amongst patients with severe haemophilia B is much lower, at 1-3%. Similar to haemophilia A, the risk of inhibitor formation is associated with mutations, that excludes expression of factor IX such as total deletions and frameshift mutations leading to stop in F IX synthesis. Inhibitors in haemophilia B are often complicated with anaphylactic symptoms occurring if the patients is challenged with factor IX concentrate. In addition, development of nephrotic syndrome may occur assuming due to immune complex disease. Fear of these serious complications has largely prevented attempts to induce immune tolerance with large doses of factor IX in haemophilia B patients with inhibitors. Management of acute bleeds in these patients may also be a difficult task. Some theoretical viewpoints will be presented during the presentation, attempting to explain the differences in immunologic response to factor VIII and factor IX in patients with haemophilia suffering from inhibitors.

New products with enhanced efficacy for treating haemophilia

Claude Negrier

Edouard Herriot Hospital, University of Lyon, France

The development of bioengineered products which have been modified to overcome their remaining therapeutic limitations represents a crucial interest to optimise haemophilia management. One of the first challenges consisted of increasing the production through modifications of the molecules and optimization of the cell culture conditions in order to allow a larger availability and diminish the production costs. The improvement of pharmacokinetic characteristics represents another challenge since the clotting factor molecules interact with several partners following injection, resulting in relatively short circulating half-lives. An increase of *in vivo* half-life would therefore prolong the intervals between the infusions and concomitantly improve the patients' quality of life through a better compliance. Different molecules have been engineered in this respect, with the aim of improving pharmacokinetic properties by enhancing resistance to degradation or diminishing clearance and ultimately prolonging the biological activity (polyethylene glycol (PEG)-coated liposomes, polysialylation, fusion proteins where the clotting factor is fused with the Fc region of IgG or with albumin in order to extend the half-life). The improvement of the haemostatic potential is another possibility through improvement of stability following activation, improvement of factor X activation capacity and increased resistance to degradation. Consequently, the mutant molecules possess an increased procoagulant activity even at lower concentrations than wild-type counterpart.

The capacity of modulating the immune response represents another area of active investigation and different options have been pursued such as differential recognition of the coagulation molecule by anti-factor VIII antibodies (recombinant porcine FVIII molecule) or decrease of the immune response efficiency by anti-idiotypic monoclonal antibodies.

In inhibitor-developing haemophiliacs, alternative treatments such as specific monoclonal antibodies have been shown to improve factor Xa generation by enhancing FIXa-catalyzed FX activation. A novel approach involved heparin-like sulfated polysaccharides (Fucoidan) which improved *in vitro* clotting time of human haemophilia A and B plasmas as well as haemostasis *in vivo* in haemophilic mice.

In the last 20 years, haemophilia management has improved dramatically through development of safe clotting factor concentrates, prophylaxis therapy and corrective surgical

interventions. Bioengineered recombinant factor concentrates with longer half-life, higher potency or lower immunogenicity will probably be available earlier than gene therapy. These achievements will significantly improve the overall compliance to therapy, while in the meantime the optimisation of the current treatment options towards a more individualised therapy will likely decrease its cost and improve the quality of life of the patients. However, these technological achievements should not mask the disparity in the availability of coagulation factor concentrates worldwide. In this regard, a potential solution could come from transgenic animals since the mammary glands of livestock can generate very high concentrations of secreted proteins.

Health Status in Older Persons with Haemophilia and how they manage their Condition

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Rationale:

Haemophilia management has radically improved in the last 30 years in Europe. Although the life expectancy of people with haemophilia (PWH) has increased enormously over the last decades, only few information are available on health status, cognitive functioning and health-related quality of life (HR-QoL) in elderly PWHs. In order to have a more precise picture of the health status and needs of these patients, a retrospective case-control study was carried out in Italy.

Methods:

Patients ≥ 65 years with severe haemophilia were investigated for health status (CIRS: Cumulative Illness Rating Scale, OJS: WFH Orthopaedic Joint Score), every day functioning (ADL: Autonomy in Daily Life, IADL: Instrumental Activity of Daily Living, TGBA: Tinetti Gait and Balance Assessment Scale), cognitive functioning (MMSE: Mini-Mental State Evaluation) and emotional well-being (Geriatric Depression Scale, HR-QoL). HR-QoL was assessed with generic (EQ-5D, WHOQOL-BREF, WHOQOL-Old) and disease-specific questionnaires (Haem-A-QoL_{Elderly}). Male controls without bleeding disorders were matched for age and geographical environment.

Results:

79.5% of the registered elderly PWHs were enrolled (n=39) with a mean age of 69.5 years (SD=3.7); 85% had haemophilia A, 13% had inhibitors, 79% received on-demand treatment,

87% suffered from chronic hepatitis C and 13% from HIV. Significantly more PHs were suffering from chronic hepatitis B, hepatitis C, HIV infection and hypertension. By contrast significantly more controls suffered from hypercholesterolemia and cardiovascular diseases. Almost all patients had arthropathy (OJS: mean=19.8, range 0-67 vs. controls mean=1.36, range 0-10). PWHs revealed worse values for ADL and TGBA, but similar for IADL and MMSE compared to controls. Regarding HR-QoL PWHs showed significantly higher impairments compared to matched controls in the dimensions 'physical health' and 'psychological' (WHOQOL-BREF), 'past activities' and 'social' (WHOQOL-OLD), and in all dimensions of the EQ-5D, but 'anxiety/depression'. PWH had significantly worse scores in the Geriatric Depression Scale.

Conclusions:

Findings of this study underline the hypothesis that elderly PWHs are in a worse health condition and show more impairments in their daily activities and HR-QoL than matched controls, but are similar in their cognitive functioning. A better understanding of physical and psychological well-being of elderly patients with haemophilia might guide interventions and plan health care in this population.

**See you at next
EAHAD Congress in
2009!**