Third and Fourth Workshops of the European paediatric network for haemophilia management.

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MEETING REPORT

Third and Fourth Workshops of the European paediatric network for haemophilia management[1]

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The meeting of 20 paediatric haemophilia treaters from 16 European countries, initiated in autumn 1997 by Dr R. Ljung, Malmo, Sweden, has become an annual meeting. The third Workshop was held in Fuschl, Austria (16–18 September 1999) and the fourth Workshop in Stresa, Italy (5–7 October 2000). The aim of each meeting is to promote informal discussion between experienced paediatric treaters on clinical practice and research to improve quality of care. The programme each year includes reviews and presentations by members of the network, in addition to invited speakers including an annual lecture on gene therapy. Reviews may be initiated in 1 year and concluded at a subsequent annual meeting. It is for this reason that we are producing a biennial meeting report and have select topics reflecting European experience.

European experience with immune tolerance induction in children with haemophilia who develop inhibitors

Dr Wolfhart Kreuz (Frankfurt/Main University, Germany) stated that the two main goals in treating inhibitor patients are: (**1**) To control severe acute bleeding; (**2**) To eradicate the inhibitor permanently by inducing immune tolerance prior to summarizing the models of immune tolerance induction used to date in Europe.

Based on the Bonn Protocol [1], the German 'Consensus recommendations' [2] and 'Guidelines' from the Federal Chamber of Physicians [3], the German Haemophilia Centre Directors published recommendations for Immune tolerance therapy (ITT) in type A haemophiliacs with inhibitors [4], recommending that immune tolerance therapy (ITT) is initiated as soon as possible after detection and measurement of inhibitor titre. If delayed, further treatment with factor VIII can boost the inhibitor titre, usually evident between days 6 and 14, and both lessen the efficacy of ITT and increase its duration. The haemophilia centre in Frankfurt has used the German high dose FVIII protocol (see Table 1 for details) to treat 21 haemophilia A patients with inhibitors and immune tolerance was achieved in 100% patients with low titre inhibitor (<5 days), and 88% patients with high titre inhibitor (>5 BU). In general about 7 months of therapy was needed for the inhibitor titre to fall below 2 BU. Even activated prothrombin complex concentrates initiated an anamnestic effect, as they may contain traces of FVIII.

The Van Creveld Clinic in Utrecht uses a low dose FVIII regimen for ITT [5] (see Table 1). This protocol has been used for 24 haemophilia A patients with inhibitors. Success (see Table 1 for criteria) was obtained in 100% of the patients with inhibitor tires <40 BU and in 75% of those with titres >40 BU.

The Malmo Protocol includes the reduction of antibodies by extracorporeal adsorption to protein A to reduce the inhibitor level. Suppression of antibody synthesis is achieved by the administration of cyclophosphamide, intravenous immunoglobulin (i.v. IgG) and high-dose FVIII [6] (see Table 1). Thirty-six attempts have been made to induce tolerance in 16 haemophilia A patients and seven haemophilia B patients with inhibitor titres >5 BU, with 62.5% of the haemophilia A patients and 86% of the haemophilia B patients becoming tolerant.

Important variables affecting outcome of ITT were found to be inhibitor titre at onset of therapy and historical maximum peak, age of patient, number of

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[1]On behalf of Members of the Network, Members of the European Paediatric Network for Haemophilia Management are given in Appendix.

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Table 1. Comparison of three European immune tolerance therapy models.

Model	Bonn–Frankfurt experience	Van Creveld	Malmo
Method	High dose FVIII and FEIBA	Low dose FVIII	Extracorporal adsorption cyclophosphamide, immunoglobulins, high dose FVIII
FVIII (IU kg^{-1}) bw	<5 BU 50–100 every 2 days >5 BU 100–200 twice daily	25 every 2 days	Mean 207 daily
ITT duration	<5 BU 1.3 months >5 BU 4 months	<40 BU 6 months >40 BU 19 months	HaemA 9–37 days HaemB 8–53 days
Criteria for success			
Recovery	Normal at 12 h	50% normal	Normal at 12 h
Half-life	Normal	>6 h	Normal
Inhibitor level	<2 BU	<2 BU	<2 BU
Amnestic response	Absent	Absent	Absent
Advantages	High elimination rate High compliance	Slightly lower costs HR poor outcome, different definition of success	Rapid No small children, severe side-effects

HR, high responder.

exposure days before onset and the inflammatory state of the patient (e.g. viral infections with fever, postoperative inflammatory response).

Results of questionnaire on treatment of children with inhibitor

Questionnaires circulated prior to the meeting were returned from 19 paediatric centres presently treating 740 haemophilia A and 118 haemophilia B boys with factor levels <1%. At the time of survey, 36 patients had inhibitors (30 with haemophilia A and six with haemophilia B). The prevalence and incidence for haemophilia patients born after 1981 was 4 and 19%, respectively, for those with haemophilia A and an identical incidence and prevalence of 5% for those with haemophilia B. Ten patients with mild or moderate haemophilia A developed an inhibitor, emphasizing that this complication does not only occur in patients with a severe clinical phenotype (factor <1%).

The definition of high and low titre differed between centres with eight defining high titre as ±5 BU, while the other ten defined high titre as ±10 BU. Of the patients with inhibitors, low titre inhibitors (>5 BU) occurred in one of 118 with haemophilia B and 62 of 740 with haemophilia A, whereas high titre inhibitors occurred in five of 118 haemophilia B and 79 of 740 with haemophilia A. When the incidence of inhibitors in children with haemophilia in this survey was compared with published series, this survey showed an incidence comparable with the three published series with the lowest incidence. The incidence of inhibitors in these series can be seen in Fig. 1.

All centres except one screen regularly for inhibitors. The interval between screening varies from three monthly in five centres, three to six monthly in eight centres, up to annually in four centres and less than annually in one centre.

It would appear that there is an increasing rate of high titre vs. low titre inhibitors as high titre inhibitors may accumulate because they do not disappear spontaneously and are sometimes resistant to immune tolerance therapy.

NovoSeven appeared to be used most frequently for serious bleeds in children with haemophilia and inhibitors. However, in Frankfurt, patients treated with plasma-derived concentrate are treated with Feiba whereas those treated with recombinant concentrate are treated with NovoSeven. Porcine FVIII is used only if patients fail to respond to FEIBA or NovoSeven.

For haemophilia A patients with low titre inhibitors, ten of 19 centres have no specific protocol but continue prophylaxis. Six centres expressed a preference for using recombinant concentrate whereas three others use either recombinant or plasma-derived concentrates.

For haemophilia A patients with high titre inhibitors, all 19 centres use ITT, 13 with recombinant concentrate, four with this or plasma-derived concentrate and two used only plasma-derived concentrates. The ITT dosing varied between centres but varied from so-called low dose 25 u kg^{-1} three times per week to high dose 200 u kg^{-1} twice each day.

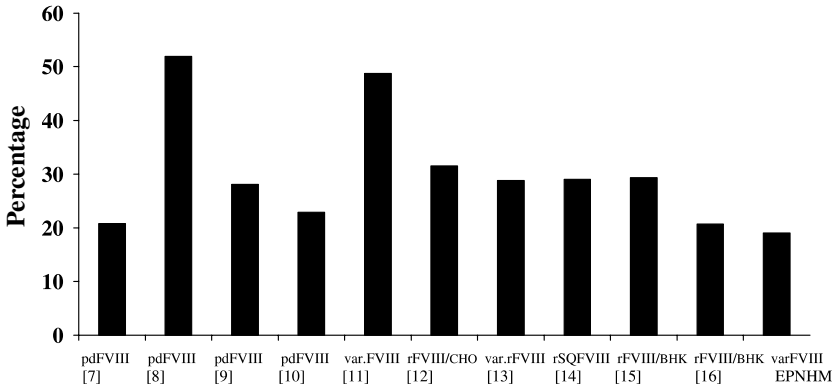

Fig. 1. Comparison of reported incidence of inhibitors in boys with haemophilia A.

[ ] = referece number; EPNHM = European Paediatric Network for Haemophilia Management; pd = plasma derived; var = various; r = recombinant

The current outcome of ITT in this survey of haemophilia A boys is that five are as yet untreated, 14 on ITT, five finished ITT without success and 61 patients have finished ITT successfully. Thus for haemophilia A patients, 72% of low titre patients had a spontaneous disappearance of the inhibitor, 92% (61 of 66) of high titre patients responded successfully to ITT. As 100% of the haemophilia B patients with inhibitors have persistence of their inhibitor.

In conclusion, this survey has shown a similar inhibitor incidence in this European paediatric haemophilia population to published studies [7–15, Bayer Inc., personal communication], (see Fig. 1), a fourfold larger incidence of inhibitors in haemophilia A compared with haemophilia B, the majority of low dose inhibitors disappear spontaneously without specific therapy whereas high titre inhibitors only disappear following ITT. The prevalence of high titre inhibitors will increase through ITT resistant cases.

With regard to screening for inhibitors, there was a range of intervals (average 5–6 months), ITT is the treatment of choice for high titre inhibitors and a broad range of ITT dosing has been used with most centres preferring to continue treating their patients with recombinant concentrate.

Haemophilia B and inhibitors

The theme of inhibitors in haemophilia was continued at the fourth Workshop with Dr Indira Warrier (Children's Hospital, Michigan, Detroit, MI, USA) giving an overview lecture on haemophilia B patients with inhibitors. The prevalence of FIX inhibitors in haemophilia B patients is 1–3% (ten times lower than FVIII inhibitors) and their likelihood of occurrence is closely associated with genotype – large deletions, frame shift and missense carry a risk of 50%, 20% and virtually none, respectively.

Obtaining the exact genotype may identify the haemophilia B patients at increased risk of anaphylaxis [16] and inhibitor development [17,18]. It has been proposed that deletions of neighbouring immune modulatory genes may be contributory factors for the development of allergic reaction against FIX.

The information on management of haemophilia B patients with inhibitors is limited because of its low prevalence.

Working groups on paediatric scoring systems

At the second workshop of the European Paediatric Network for Haemophilia Management 1998 in Vitznau, it was agreed that two working groups would propose revised orthopaedic and radiological scoring system for children [19].

Dr Pia Petrini (Karolinska Hospital, Stockholm, Sweden) introduced a new orthopaedic scoring system at the Third Workshop (Fig. 2) using clinical parameters and scores adapted from the World Federation of Haemophilia (WFH) scoring system. Clinical parameters (swelling, muscle atrophy, crepitus on motion and flexion contracture) have three instead of two grades and range of motion was subdivided by degree instead of per cent. Axial deformity and instability were replaced by gait and strength against gravity. Parameters to describe a target joint and a joint with chronic synovitis have also been added.

A prospective study for the group was designed to confirm these preliminary findings at the Stockholm centre (see Table 2).

Five centres of the network (Athens, Utrecht, Marseilles, Malmö and , Stockholm) provided data for the fourth Workshop confirming the preliminary findings. The comparison of the original WFH scoring system and the new scoring system developed

	LA	RA	LE	RE	LK	RK	Comments
Target joint							
Chronic synovitis							
Pain							
Gait							
Strength							
Muscle atrophy							
Swellings							
Range of motion							
Flexion contracture							
Crepitus on motion							
TOTAL							

Name…..……..……..Date……..…….Investigator……..……

SWELLING
0 = None
1 = Mild
2 = Moderate–severe

PAIN
0 = No pain
1 = Light pain or stiffness
2 = Moderate pain with or without activity
3 = Severe pain limiting normal activity for age

MUSCLE ATROPHY
0 = None
1 = Mild
2 = Severe

GAIT: Abnormalities=limping, walking with foot turned out, walking on side foot, no push-off, walking on toes, uneven strides, no/uneven weight shifting, abnormal running, galloping or skipping

CREPITUS OF MOTION
0 = None
1 = Mild
2 = Severe

0 = Normal walking, running, skipping, galloping
1 = Normal walking, abnormal running or skipping
2 = Abnormal walking and 1-2 of above gait abnormalities
3 = Abnormal walking and 3 or more of above abnormalities

RANGE OF MOTION
0 = No loss
1 = Loss of $\leq 10^{o}$
2 = Loss of $>10^{o}$

STRENGTH
Against gravity
0 = Moves through full range, takes, maximal resistance
1 = Moves through full range, takes, minimal resistance
2 = Moves through full range
3 = Unable to move through full range

FLEXION CONTRACTURE
0 = normal
1 = 0–10°
2 = loss of >10°

3 = **TARGET JOINT** (3 bleedings in one joint in 6 months)

3 = **JOINT WITH CHRONIC SYNOVITIS** (effusion >6 months)

Fig. 2. Orthopaedic scoring system for examination of paediatric haemophilia patients.

especially for paediatric needs included a total of 116 haemophilia A and B patients aged 4–18 years, 56 on primary prophylaxis, 36 on secondary prophylaxis (including 26 on long- term secondary prophylaxis) and 24 on demand treatment (including 16 patients with moderate haemophilia). The two scoring systems were applied to this patient population stratified into three age groups, 4–8, 9–13 and 14–18 years. On primary prophylaxis, all except two children of the oldest age group scored zero in both systems. On secondary prophylaxis, the age-matched mean score value by the new system was always higher than the score on the old system. Both scores increase with age. The same tendency was observed with patients treated on demand, but the mean scores even in patients with moderate haemophilia were always higher as compared with patients on secondary prophylaxis. In summary, the new scoring system reflected pathological alterations more sensitively.

At the second workshop, it was also decided to initiate a further workgroup to develop a scoring system for magnetic resonance imaging (MRI).

Table 2. Scores obtained using new paediatric orthopaedic and WFH orthopaedic clinical scoring systems for individual children of shown age group.

Age range (years)	Orthopaedic score for individuals by new paediatric	Orthopaedic score for individuals by WFH	X-ray changes
3–7	26	7	No
	21	7	No
	6	1	No
	3	0	No
	20	4	No
8–12	4	1	Yes
	4	2	No
	7	2	No
13–18	3	0	No
	8	1	Yes
	23	6	Yes
	13	2	Yes
	10	2	Yes
	4	2	No
	6	4	No
	6	1	No

Dr B. Lundin (University Hospital, Lund, Sweden) was to plan a multicentre project including 5–15-year-old children, whose ankle joints would be examined by MRI to evaluate changes in synovia, subchondral bone, and joint cartilage. Participants were to send a complete MRI investigation of at least one volunteer with normal X-rays to Lund.

At the fourth Workshop Dr Lundin presented preliminary data on 16 MRI scans and derived a detailed scoring system which was to be tested for its usefulness by other participating centres who were to submit MRI scans of ankle joints from a further 50 haemophilic boys of mixed ages. Additionally comparing this new scoring system with the conventional radiological scores, it is proposed to evaluate scores in relation to patient age and treatment history. It is hoped that this will inform future practice and treatment selection in preventing haemophilic arthropathy.

Carrier and prenatal diagnosis of haemophilia

Dr Johannes Oldenburg (University of Bonn, Germany) described the laboratory techniques for genotype assessment in haemophilia and for providing a certain diagnosis of carriership and accurate and early prenatal diagnosis of haemophilia A.

In 369 German haemophiliacs the intron 22 inversion was found in about 33% of the patients, missense mutations in another 33% and small deletions, nonsense mutations, splice sites, large deletions or small insertions in a total of 25%. In 10% of the analyses no mutations could be found. Analysis of the distribution of mutations within the FVIII gene reveals three so-called hotspots in exons 11, 14 and 23. The highest rate of mutations were found in exon 14 (20%) which were mostly caused by small deletions and insertions or by missense mutations.

The experience of carrier and prenatal diagnosis in Italy was presented by Dr Pier Giorgio Mori. A questionnaire addressed to haemophilia A carriers in Italy has been initiated to collect data about the general attitude towards pregnancy (religious and personal beliefs), experiences in the management of haemophilia in the family, knowledge of haemophilia and the influence of the carrier status on reproductivity. Dr Mori was interested to know if the network members would like to use this as the basis for a European study.

Annual lectures on gene therapy

At the third Workshop Dr Van Den Driessche (Transgene Technology and Gene Therapy, Leuven, the Netherlands) gave an overview of the status of gene therapy for haemophilia in 1999, while at the fourth Workshop, Mike Fournel (Bayer, USA) outlined the rationale of gene therapy and summarized the status of preclinical and clinical trials as of September 2000.

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Appendix

1999 and 2000 Members of the European Paediatric Network for Haemophilia Management

Aronis-Vournas, Sophie, Athens, Greece[2], Kurnick-Auberger, Karin, Munich, Germany[2], Van den Berg, Marijke, Utrecht, The Netherlands[3], Chambost, Herve, Marseille, France[2], Claeyssens, Segolene, Toulouse, France[2], Van Geet, Christine, Leuven, Belgium[2], Glomstein, Anders, Oslo, Norway, Hann, Ian, London, UK, Hill, Frank, Birmingham, UK[2], Kobelt, Rainer, Bern, Switzerland[2], Kreuz, Wolfhart, Frankfurt, Germany[2], Ljung, Rolf, Malmo, Sweden[2],

[2]Present at the 3rd and 4th Workshop.
[3]Present at 3rd Workshop only.

Muntean, Wolfgang, Graz, Austria[2], Petrini, Pia, Stockholm, Sweden[2], Rosado, Lino, Lisboa, Portugal[2], Scheibel, Elma, Copenhagen, Denmark[2], Siimes, Martti, Helsinki, Finland[2], Smith, Owen, Dublin, Ireland[2], Tusell, Joan, Barcelona, Spain[2].

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