ORGANISATION MONDIALE DE LA SANTE

WHO/HDP/WFH/94.6
ENGLISH ONLY

HEREDITARY DISEASES PROGRAMME
DIVISION OF NONCOMMUNICABLE DISEASES

Geneva, 21-23 March 1994

REPORT OF A JOINT WHO/WFH MEETING ON THE CONTROL OF HAEMOPHILIA: MODERN TREATMENT OF HAEMOPHILIA

List of Contents

/...

List of Contents, continued

1. INTRODUCTION

The World Health Organization (WHO) and the World Federation of Hemophilia (WFH) have considered the problems of haemophilia at joint meetings, and have issued reports on the possibilities for the prevention and control of haemophilia[1] and carrier detection and prenatal diagnosis[2]. With rapidly expanding technology in many areas (both diagnostic and therapeutic) and continued problems and challenges concerning joint disease, transfusion-transmitted diseases, inhibitors, provision of care in developing countries, and education and cost issues, a joint meeting was held in Geneva from 21-23 March 1994 to discuss and review those issues surrounding current and future management of haemophilia and its complications, including prospects for genetic technology and gene therapy for both developed and developing countries. Following an in-depth discussion of each topic, the group developed a series of recommendations.

2. THE ROLE OF PRIMARY PROPHYLAXIS IN HAEMOPHILIA CARE

While many persons with haemophilia who received blood products between 1979-1984 have already succumbed to the acquired immune deficiency syndrome (AIDS), many are still surviving but have human immunodeficiency virus (HIV) infection and declining cellular immunity, with or without AIDS defining illness. Many of these individuals are also hepatitis C virus (HCV) antibody positive. There is no cure for either of these blood borne viral illnesses, thus finding more effective modes of treatment remains a necessity.

Fortunately, with only a few notable exceptions, there have been no new cases of HIV infection resulting from transfusion of blood or clotting factor concentrates for several years, (and seemingly much more virally safe clotting factor concentrates in general). Thus more attention can be focused on other problems and questions, such as the pros and cons of prophylaxis, in an attempt to prevent joint disease, choice of an expanding array of products, what can be done to prevent or eradicate inhibitors, prospects for a cure via gene therapy, and how can persons with haemophilia residing in developing countries best be managed with available resources.

2.1 Rationale and experience to date

What is the role of primary prophylaxis in haemophilia care? The prevention of joint and musculoskeletal disease in severe haemophiliacs has been accomplished by physicians in Sweden by starting prophylaxis early in life (age 1-2 years), with dosages and dosage intervals aimed at keeping trough levels of Factor (F) VIII or F IX above 1%. The rationale for keeping trough levels just above 1% is that persons with greater than 1% F VIII or F IX have far fewer bleeding episodes and a much milder clinical course than do patients with severe haemophilia (who have less than 1% F VIII or F IX).

---

[1] Report of a Joint WHO/WFH Meeting on the Possibilities for the Prevention and Control of Haemophilia, Geneva, 26-28 March 1990 (WHO/HDP/WFH/90.3). Copies of the report are available free of charge from the Hereditary Diseases Programme, Division of Noncommunicable Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland.

[2] Report of a Joint WHO/WFH Meeting on the Control of Haemophilia: Carrier Detection and Prenatal Diagnosis, Geneva, 10-12 February 1992 (WHO/HDP/WFH/92.4). Copies of the report are available free of charge from the Hereditary Diseases Programme, Division of Noncommunicable Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland.

While several groups of investigators have reported small series of patients utilizing various prophylactic regimens, the most comprehensive experience reported to date has come from Malmö, Sweden. Nilsson and co-workers have published twenty five years' experience with prophylaxis in 60 patients with severe haemophilia A and B.[1] Over the 25 year period, prophylaxis has been intensified, by starting it at an earlier age and by increasing the dosage of F VIII or F IX. As a result, their most recent subset of 15 boys (now ages 4 to 12 years), who were started on prophylaxis at age 1-2 years, have had no episodes of joint bleeding and have excellent orthopaedic and radiological joint scores (all zero).[1]

2.2 Recommendations in the USA and Canada

After an in-depth review of the Swedish experience with primary prophylaxis, in early 1994 the National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) in the USA recommended that primary prophylaxis be considered optimal therapy for persons with severe haemophilia (F VIII or F IX levels $<1\%$), beginning at an early age (1-2 years). The MASAC document also contains a recommendation that a mechanism be developed to periodically evaluate joint status, to document any complications, and to document all costs associated with each child's prophylaxis. It is also recommended that risks versus benefits, and all possible problems associated with prophylaxis be discussed with each family (including venous access problems and complications which may result from indwelling central venous catheters) [2].

Again, based mainly on the excellent results in Sweden, the Canadian Hemophilia Society's most recently approved Blood and Coagulation Products Policy document (dated 16 May 1993) included a recommendation that prophylactic treatment be offered for all young children with severe haemophilia.

2.3 Cost *vs* benefit

While there has been concern that primary prophylaxis may be considerably more costly than episodic ("on demand") treatment, this is not necessarily the case. Carlsson et al have investigated the use of individual pharmacokinetics as an aid in determining the optimal dosage of F VIII for each patient, with emphasis on the impact of different dosage regimens on cost. These investigators found that a dosing of F VIII according to kinetic principles can result in more cost-effective utilization of clotting factor [3]. Additionally, there should be much less time lost from school or work, fewer costly emergency room visits, fewer hospitalizations, less need for orthopaedic interventions, and enhanced self esteem if joint bleeding and haemophilic arthropathy can be prevented. One would hope that centres beginning primary prophylaxis programmes (or controlled studies of primary prophylaxis versus episodic treatment) will prospectively incorporate well designed cost/benefit analyses so that one will ultimately know the overall relative costs of primary prophylaxis versus "on demand" treatment.

2.4 Recommendations

Since the main goal is to prevent joint bleeding and its sequelae, prophylaxis should be considered optimal management for persons with severe haemophilia A and B (baseline level $<1\%$ F VIII or F IX). Treatment should be started at the age of 1-2

years and continued indefinitely. Where prophylaxis is not feasible or appropriate, "on demand" therapy should be given as early as possible, at the on-set of a bleeding episode.

3. VIRAL SAFETY OF CURRENTLY AVAILABLE PRODUCTS

3.1 Donor screening and virucidal methods

Although clotting factor concentrates are still produced from plasma collected from thousands of donors, the recognition of the high rates of transmission of hepatitis viruses (particularly HCV and HBV) and HIV by these products stimulated the development of safer concentrates during the 1980s.

Improved screening of blood and plasmapheresis donors and a variety of viral attenuation methods have resulted in plasma-derived F VIII and F IX concentrates which are considerably safer than ever before. Mandatory donor screening for HIV-1 and 2, and HCV seropositivity [4] and for HB surface antigen (HB_sAg) greatly reduces the viral burden of starting plasma from which F VIII and F IX concentrates are made. In most countries, virucidal methods *must* be used in the preparation of all licensed F VIII and F IX concentrates. Methodologies include terminal heating of the lyophilized products at 80°C ("dry heating"), heating in solution at 60°C in the presence of stabilizers (pasteurization), heating in a suspension containing the organic solvent n-heptane, or with hot vapour under high pressure, or adding a detergent/solvent mixture during manufacture.[5,6]

3.2 Evidence for viral safety and for continued transmission of certain viruses

While many of the currently available concentrates have been subjected to viral safety studies in haemophilic patients who had no previous exposure to blood products, many others have not. For the latter, one can only draw inferences from studies of another product treated with very similar virucidal methodology. Additionally, while published cases of viral infections occurring in patients not enrolled in prospective viral safety studies may be more difficult to evaluate (in terms of cause and effect), they can provide useful information. For example, recent reports of hepatitis A in 85 European haemophiliacs (from Belgium, Germany, Ireland and Italy) who had received a solvent/detergent treated F VIII concentrate, clearly indicated that solvent/detergent treatment cannot inactivate non-lipid enveloped viruses [7,8]. Another non-enveloped virus, human parvovirus B 19, has also caused infection in a number of persons with haemophilia infused with concentrates which were pasteurized, vapour-treated or solvent/detergent treated [6,9-11]. It appears that none of the current virucidal methods are effective against parvovirus B 19, which can cause such serious complications as bone marrow failure and chronic anaemia in immunocompromised individuals and hydrops fetalis in pregnant women [6,12,13].

3.3 Need for additional strategies to protect recipients from blood-borne viruses

It seems plausible that other pathogenic viruses with features similar to HAV and human parvovirus B 19 may exist, and may enter the blood supply. It was unanimously agreed at this meeting that no one should abandon the goal of absolute safety! Manufacturers should vigorously pursue strategies aimed at preventing viral contamination of concentrates, while federal regulatory agencies should safeguard patients by setting rigorous safety standards.

Additional measures should include protection of recipients by vaccination against hepatitis A and B, rigorous donor selection and screening, and seroconversion surveillance programmes aimed at detecting any product which may be transmitting a blood-borne virus.

In view of the fact that fresh frozen plasma (FFP) and cryoprecipitates are still used in many parts of the world, virucidal methods applicable to these products must be further developed and studied in susceptible haemophilic recipients.

3.4 Role of recombinant clotting concentrates

Where available and affordable, recombinant (r) F VIII concentrates would seem to be preferable to human plasma-derived products, due to their added margin of viral safety. Recombinant F VIII has been in use in human subjects since 1987 and to date, both manufacturers' products Miles'Kogenate™ and Baxter's Recombinate™ have had an excellent track record of safety. (It should also be noted a third rF VIII concentrate, Kabi Pharmacia's deletion product, rF VIII-SQ, has been in prelicensure clinical trials in Europe since March 1993). Although one must keep in mind the *theoretical* risk of transmission of other viruses which might be associated with mammalian cell cultures, bovine albumin or murine monoclonal antibodies, rF VIII would seem to offer not only viral safety, efficacy and a very low incidence of minor side effects, but the possibility of an unlimited supply as well.

At the present time there are no available rF IX concentrates. However at least one rF Ix concentrate (produced by Genetics Institute, Cambridge, MA, USA), is undergoing development.

3.5 Recommendations

(1) Plasma-derived coagulation F VIII concentrates, treated with the currently available virucidal methods, carry a low risk of transmitting HIV and hepatitis B and C viruses. (2) Manufacturers of blood products should pursue the development of virucidal methods to inactivate blood-borne viruses resistant to current virucidal methods. (3) The viral safety of clotting factor concentrates for use in haemophilia B is less well established. (4) For all products (both plasma-derived and recombinant), continuing surveillance concerning viral safety is needed.

4. CHOICE OF PRODUCT FOR TREATING OR PREVENTING BLEEDING IN PERSONS WITH HAEMOPHILIA A OR B

4.1 Types of products

While certainly not true world-wide, in many countries there are now many types of products to choose from. Products are plasma derived or recombinant, they are subjected to various types of viral attenuation procedures, and they differ in purity. In choosing a product one is generally influenced by perceived viral safety, efficacy, availability, purity, cost, and ease of handling (storage, mixing and administration). Assuming that the full array of products are available, and that all are equally effective, viral safety and cost would be the major determinants. As noted earlier, currently available virally attenuated plasma derived products carry a negligible risk of transmitting

HIV and a very low risk of transmitting hepatitis B and C. However, they may transmit other blood borne viruses such as human parvovirus B 19. Although currently produced virally attenuated plasma-derived concentrates appear to be reasonably safe, rF VIII provides an extra margin of viral safety and thus would be preferred if affordable. At present, there is no licensed rF IX product (although at least one is in development).

4.2 Product considerations for haemophilia B

For persons with haemophilia B another safety issue to be considered is that of thrombogenicity.[5,14] The F IX complex concentrates (the so-called, "prothrombin complex concentrates," or PCCs) can, on occasion, result in deep venous thrombosis, pulmonary embolism and/or disseminated intravascular coagulation, particularly in persons undergoing orthopaedic surgical procedures, in those with crush injures or large intramuscular haemorrhages, in those with significant hepatocellular disease and in neonates. In such situations it is recommended that one of the high purity, "coagulation F IX concentrates" be used rather than PCC. While considerably more expensive than PCC the high purity F IX products may be quite cost effective if thromboembolic complications can be avoided.

4.3 Product purity considerations

What about product purity? While purer would seem to be better, is there evidence to support this notion, especially considering the higher costs of so-called ultrapure products? During purification processes used (ex: immunoaffinity purification of plasma-derived F VIII and F IX concentrates), several logs of virus are lost. Thus, whatever viral attenuation process is being used, there is less virus contamination of the starting material. Additionally, several studies have shown that cellular immunity is better preserved in HIV seropositive individuals treated with immunoaffinity purified F VIII concentrates than with intermediate purity F VIII concentrates [15,16].

4.4 Use of DDAVP

For persons with mild or moderate haemophilia A, 1-deamino-8-D-arginine vasopressin (DDAVP), is regarded as the treatment of choice. This synthetic agent effects a rapid 2-10 fold (average 3 fold) increase in F VIII (and vWF), and is available in several formulations. While the drug is generally given intravenously (in a dosage of 0.3 μg/kg) for surgical procedures or other in-hospital uses, for home-use the highly concentrated intranasal spray formulation is ideal. Side effects are uncommon as long as certain precautions are observed. One must keep in mind that DDAVP is a potent antidiuretic agent; thus hyponatremia and water intoxication may occur. [17,18].

4.5 Recommendations

(1) For persons with haemophilia A, viral safety should be the primary criterion of choice among available products. (2) For persons who are HIV seropositive, the use of immunoaffinity purified and recombinant F VIII concentrates are recommended. (3) For persons with mild or moderate haemophilia A, DDAVP should be used whenever appropriate. (4) For persons with haemophilia B, high purity F IX concentrates should be used in specific circumstances associated with a high risk of thrombotic complications. In all other situations, the use of prothrombin complex concentrates can be considered as well.

5. OPTIMAL DOSAGES OF PRODUCT

5.1 Guidelines

Perhaps surprisingly, there is no consensus concerning optimal dosage of F VIII or F IX for treatment (or prevention) of the various types of bleeding which may occur in persons with haemophilia (i.e., what dosage is sufficient to control bleeding without being excessive). Published formulae allow one to calculate what dosage should be used to achieve a certain value of F VIII or F IX in the recipient, and published determinations of half-life for infused F VIII and F IX may be used to determine dosage intervals. While these are not absolute and may vary slightly from patient to patient and perhaps from product to product[19] as well, they are useful guidelines.

On the other hand, the optimal therapeutic level for control of even such common types of bleeding as acute haemarthrosis remains debatable. Thus Rickard has provided a recommended *range* of dosages for each type of bleeding[20]. One can reasonably assume that less treatment will be required if a contained hemorrhage (ex, acute haemarthrosis, iliopsoas hemorrhage) is treated early. Thus prompt recognition and treatment of a bleeding episode can save clotting factor as well as musculoskeletal function. Ancillary measures such as rest of the affected part, and use of an antifibrinolytic agent for invasive dentistry or other bleeding in the oral cavity are, of course, extremely important as well.

5.2 Surgery

For surgical procedures one must ensure appropriate communication and planning between medical staff, surgeon, and coagulation technologist. The patient's inhibitor status must be known *before* surgery is planned. Whenever possible, following an initial bolus dose, clotting factor should be given by continuous infusion.[20,21] This will not only prevent hazardously low trough levels from delays in infusing follow-up doses, but will often result in less clotting factor being used, and makes it possible to monitor F VIII or F IX levels at any time.

5.3 Recommendations

(1) For the haemostatic management of the person with haemophilia, an accurate assessment of the level of F VIII or F IX is essential. (2) Episodes of bleeding in haemophilia require therapy with F VIII or F IX replacement. This therapy must be safe, administered promptly, and continued for a sufficient duration to fully control the bleeding episode. (3) Surgery in haemophilia should only be undertaken after the exclusion of an inhibitor and when sufficient supplies of the necessary therapeutic products are available to cover the operative and postoperative periods. Such procedures require close cooperation between the physician, the blood bank or pharmacy, the surgeon and coagulation laboratory personnel.

6. MANAGEMENT OF HAEMOPHILIACS WITH INHIBITORS

6.1 Extent of problem and risk factors for development of inhibitors

Inhibitor antibodies to F VIII develop in 15-35% of persons with haemophilia A. Most develop in those with severe haemophilia A (< 1% F VIII), and most develop early in life, after relatively few exposure days to F VIII. In each of 3 recently published prospective studies (two with rF VIII preparations[22,23] and one in which patients had been treated predominantly with intermediate purity, plasma-derived F VIII [24]), those who developed inhibitors did so after a median of 9-11 exposure days. In addition to age and severity of haemophilia, other patient risk factors for inhibitor development include type of gene defect (ex, large gene deletions, stop codons, nonsense mutations), a family history of inhibitors, and race. In only one instance has a particular product been implicated in causing inhibitor development [25].

6.2 Detection and quantitation of inhibitors

Those centres evaluating and treating persons with haemophilia must have the capability of detecting and quantitating inhibitors. Laboratory screening can be done using a modification of the activated partial thromboplastin time (APTT); for quantitation of an inhibitor, the Bethesda Assay is recommended [26]. In order to determine whether or not porcine F VIII is a therapeutic option for a particular patient with an inhibitor, porcine F VIII can be substituted for human F VIII in the Bethesda assay [26].

6.3 Low and high responders

While patients who form inhibitor antibodies in low concentration only, ie, <5 B.U. (so-called "low responders"), can generally be managed with F VIII in usual or slightly increased dosage, those who produce inhibitor antibodies in higher concentrations usually cannot. It is these persons who are particularly difficult to manage.

6.4 Therapeutic options for treating bleeding episodes in high responders

Therapeutic options for bleeding episodes in high responder inhibitor patients include high dose, human or recombinant factor VIII concentrates, sometimes given by infusion, F IX complex concentrates (prothrombin complex concentrates, PCCs), either standard or purposely activated PCC (APCC), porcine F VIII, or the investigational agent, rF VIIa (Novo Seven,™ Novo-Nordisk, Gentofte, Denmark). Most use PCC or APCC in a dosage of 75 U per Kg as first line treatment for bleeding episodes, although it is recognized that these products are not as effective as is F VIII in a non-inhibitor patient, and they cannot be relied upon to prevent or control bleeding. Other disadvantages of PCCs and APCCs include the fact that their precise mechanism(s) of action are unknown, there are no laboratory parameters by which their effectiveness can be measured, and large, repetitive doses may be hazardous. It should be noted that there have been over 20 reports of acute myocardial infarction in relatively young haemophilic patients with inhibitors following treatment with PCCs [5,14].

The highly purified porcine F VIII preparation, Hyate:C (Speywood Pharmaceuticals, Wrexham, UK) can be quite effective in patients whose inhibitors have little or no cross-reactivity with porcine F VIII [27,28]. Advantages include a high rate of success in controlling or preventing bleeding in properly selected patients, and the fact

that one can measure and follow the recipient's F VIII response. Since it is a foreign species protein, disadvantages include the risk of allergic reactions, rarely anaphylaxis. Allergic reactions can be minimized or prevented by premedicating the recipient with 100 mg intravenous hydrocortisone. While Hyate:C is being used for home treatment in selected patients in the UK, most reserve its use for surgical procedures or in hospital management of more serious bleeding episodes.

Although not yet licensed for use, Novo Seven ™(rF VIIa) has proven to be effective in controlling bleeding in over 100 patients on a compassionate use basis (in patients who had failed to respond to other therapeutic measures). rF VIIa has a short half-life (2-4 hours); thus repeat doses, if necessary, must be given every 2-3 hours [29]. This product has not yet been evaluated in the home treatment setting. Thus whether or not it will prove to be more effective than PCCs or APCCs for early treatment of acute haemarthrosis is unknown at present.

6.5 Immune tolerance regimens

In view of the limitations of available treatment modalities for bleeding in inhibitor patients, there has been considerable interest in attempting to induce immune tolerance to F VIII (or F IX). Now that safer clotting factor concentrates are available, various immune tolerance induction (ITI) regimens have been developed and tried in infants and children as well as adults with F VIII or F IX inhibitors. Many of the ITI regimens in current use employ F VIII alone, generally starting with large daily doses of F VIII. However some groups (such as physicians in The Netherlands) have induced tolerance with much lower doses of F VIII. Others include corticosteroids or intravenous gamma globulin (IVIG) and cyclophosphamide in addition to F VIII [29]. While many patients have had good responses, most appear to require some sort of prophylaxis (regularly scheduled infusions) in order to maintain suppression of their inhibitor antibody. Nonetheless, it is noteworthy that in a multicentre study of 18 patients originally tolerized with Brackmann's "Bonn Protocol" several years earlier, Sultan and co-workers found that 8 still had undetectable or very low levels of inhibitor and had no anamnestic responses to infused F VIII.[31] On behalf of the International Society on Thrombosis & Haemostasis F VIII & F IX Subcommittee, Mariani and Ghiardini are maintaining a registry of ITI regimens and patient responses, in an attempt to determine which regimen is most effective.[32] In another attempt to answer this question, DiMichele and colleagues in the USA have developed a randomized, controlled trial aimed at comparing responses to daily doses of F VIII alone vs F VIII plus a short course of IVIG and cyclophosphamide. These questions are extremely important, and it is hoped that analysis of data from Mariani's registry, and from the randomized, controlled trial, will provide us with clinically useful guidelines for ITI.

Other ongoing studies are aimed at elucidating the underlying immune mechanisms involved in inhibitor antibody development, disappearance, and induction of immune tolerance. An additional area of interest is the development of immune tolerance to F VIII in fetuses known to be at risk of inhibitor development (i.e., those with large gene deletions or family history of high titer inhibitors).

6.6 Recommendations

(1) Diagnosis and treatment of inhibitors should be carried out in comprehensive haemophilia centres with adequate laboratory quality control and blood

product support. Once an inhibitor is diagnosed, immune tolerance should be considered as soon as possible. In children this may necessitate the placement of a central venous catheter for appropriate venous access. (2) In a patient with an inhibitor the benefits and risks of elective surgery should be carefully considered. Surgery should only be done in a comprehensive haemophilia centre and only after consultation and planning between the surgeon and appropriate members of the haemophilia team.

7. MANAGEMENT OF PATIENTS WITH HIV INFECTION AND/OR HEPATITIS

7.1 Extent of problem - HIV and AIDS

It is estimated that approximately 8,500 individuals in the USA became HIV infected via clotting factor concentrates between 1978 and 1984; at least 4,000 of these have developed AIDS. With the exception of a small outbreak of cases reported in 1990 [33], no new cases of seroconversion have been reported in North America or Europe since 1986. However, in some parts of the world where non-virally attenuated products are still being used new HIV infections are no doubt still occurring.

7.2 Need for proper evaluation, treatment and counselling

It is extremely important that those who are infected with HIV be properly evaluated, counselled, followed and treated by health care professionals who are knowledgeable in this area. While there is still no cure for HIV infection, as study data accrue, treatment recommendations change. At present it appears that drug combinations are likely to be more effective than single agents; combinations of various drugs with zidovudine produce a more sustained fall in HIV viral load and a more sustained rise in CD4 counts.

Prophylaxis is important in the prevention of opportunistic infections such as Pneumocystis carinii pneumonia (PCP), toxoplasmosis, Mycobacterium avium complex, and fungal infections [34], and can certainly improve quality of life. However, those managing HIV infected individuals must keep themselves updated on changing recommendations concerning when to institute prophylaxis and which drugs are most effective. As noted by Lee [35], with more widespread use of prophylaxis, it is also likely that drug resistance will increase for each pathogen.

Education and counselling are important as well. Proper handling of needles, syringes, blood and body fluids can prevent secondary cases, as can education and counselling concerning sexual transmission of HIV. In USA studies an estimated 10-15% of regular sexual partners of HIV infected haemophiliacs became infected, as did a number of infants born to HIV infected mothers.

7.3 Viral hepatitis

Hepatitis A, B, C and D have all been transmitted by blood products to varying extents. While hepatitis A does not result in chronic infection, recently reported outbreaks of hepatitis A resulting from solvent-detergent treated clotting factor concentrates highlighted the fact that certain blood-borne viruses (non-lipid coated viruses such as HAV and human parvovirus B 19) are not being killed by viral attenuation methods in current use [6-11, 36). Vaccines are available and are recommended for prevention of HAV and HBV infection (although a HAV vaccine is not yet licensed in the

USA), and only those persons who are persistently HBs antigen positive are susceptible to HDV infection [37].

While serologic tests for screening blood and plasmapheresis donors for HBsAg have been available since the 1970s [5], an antibody test for HCV was not introduced until 1990 [4,5]. Several studies of North American and European haemophilia populations then documented extremely high rates of HCV seropositivity [4,5,38]. It now appears that most (if not all) HCV infected individuals do not develop immunity but rather, have ongoing viral replication and can progress to chronic hepatitis. Some will develop end-stage liver disease or hepatocellular carcinoma many years later [3-40]. Those treating persons with haemophilia and HCV seropositivity must now decide if and when to intervene with liver biopsy and/or alpha interferon [39], and what to tell the patient and his family concerning prognosis and expected response to treatment. While interferon often results in improvement in liver pathology and liver enzymes, beneficial effects may be short-lived once therapy is stopped. For the person who is dually infected with HIV and HCV, the likelihood of progression to liver failure is greater (twenty-fold greater) than with HCV infection alone [35]. This may well reflect increased HCV replication resulting from the immunosuppressive effects of HIV infection.

7.4 Recommendations

HIV and hepatitis: (1) Individuals with haemophilia and their sexual partners should be tested for HIV-1, HBV and HCV. (2) Vaccination against HBV should be given to susceptible individuals. (3) Within the comprehensive care setting clinical and laboratory monitoring of these transfusion transmitted viral diseases should be undertaken regularly, and appropriate prophylactic and antiviral therapy given.

8. MANAGEMENT OF HAEMOPHILIA IN DEVELOPING COUNTRIES WITH AVAILABLE RESOURCES

8.1 Extent of problem

Management of haemophilia in less developed countries presents formidable challenges. Governmental and family monetary resources are usually woefully inadequate, knowledge and awareness of haemophilia and its management are often non-existent, there is often no access to proper diagnostic testing, and therapeutic material is inadequate - not only in quantity but in viral safety. While there is heterogeneity in the population (and from country to country) with regard to income, education, and motivation, it is estimated that less than 5% of the population in less developed parts of the world could provide treatment for a haemophiliac son comparable to that available in the developed world [41].

8.2 Need for education

Education is of utmost importance. There must be greater awareness about haemophilia and its management, not only by health care workers, but by the patient and his family. As noted by Jones [40], patient and family education remains the single most important weapon against haemophilia and its complications. The World Federation of Hemophilia, through its national member organizations should take an active lead in this

area, by developing educational programmes, literature and audiovisual materials which are culturally, socio-economically and language appropriate.

8.3 Need for regional reference centres

There should also be regional reference centres with experienced and knowledgeable health care professionals who can coordinate haemophilia services for a geographic region. Such reference centres should have diagnostic laboratory capabilities, as well as persons knowledgeable in the evaluation and medical and surgical care of persons with haemophilia, and a modern and well-equipped blood bank which is capable of preparing and storing fresh frozen plasma and cryoprecipitate. The regional reference centre should provide educational services as well, for both patients and other health care providers.

In order to prevent new cases of transfusion-transmitted HIV infection, blood and plasma must be adequately screened, and virucidal methods should be developed and instituted for plasma and cryoprecipitates (ex: solvent/detergent treatment of plasma and heat treatment of cryoprecipitates). Manufacturers and others in more developed countries should help by making available virally attenuated clotting factor concentrates through the WFH and WHO - in fact, it is very encouraging to see that this has begun to happen as a result of one action of WFH's Decade Plan [43].

Additionally, countries with some infrastructure and resources should be encouraged and given the technical help to produce recombinant F VIII. Although one can argue that this is not realistic at present, one should never abandon the goal of providing adequate amounts of a safe product to all persons with haemophilia. Recombinant technology not only provides an added margin of viral safety, but the possibility of an unlimited supply.

In the interim, while therapeutic materials remain scarce and are often unattainable, families and health care providers should be instructed in the use of such supportive measures for joint and muscle bleeding as application if ice packs and rest of the affected part, and appropriate analgesics.

8.4 Recommendations

(1) Developing countries should set up coagulation reference centres situated in tertiary medical facilities to coordinate services for patients with haemophilia and other disorders of haemostasis. (2) Haemophilia services should be integrated with the existing health care infrastructure. A model is suggested which can be suitably modified in each country [41]. (3) Developing countries should seize the initiative made imperative by the HIV epidemic to strengthen blood transfusion services and coordinate the transfusion service with haemophilia and thalassaemia services. 4) Since self sufficiency for coagulation factors through blood donation will take time, and in view of viral safety issues, developing countries with the necessary infrastructure should explore the possibility of producing recombinant coagulation factors.

9. GENE THERAPY

9.1 Technological advances and problems to be solved

In stark contrast to the current status of haemophilia care in less developed countries, there has been considerable enthusiasm and excitement about the rapid technologic advances of recent years which have brought us recombinant clotting factor concentrates (rF VIII, rF IX, rF VIIa and the deletion F VIII product, rF VIII SQ, which lacks the B-domain) as well as direct detection of defects in the F VIII and F IX genes, allowing accurate carrier detection and prenatal diagnosis.

The cloning of the F VIII and F IX genes and their expression in mammalian cells also introduced the possibility of a cure for haemophilia A and B via gene therapy. The introduction of normal F VIII or F IX genes into persons with haemophilia would, theoretically, result in expression of the normal gene and the release of normal F VIII (or F IX) into the circulation. Depending on the level of F VIII (or F IX) attained and maintained, gene therapy could either partially or completely cure the person's haemophilia.

While the full F VIII DNA is too large (8.8 kilobases) to be incorporated into retroviral and adenoviral vectors, and thus cannot be efficiently transduced by these vectors a cDNA with most of the B encoding domain deleted (ΔB F VIII ~ is 5.7 Kb in length) can be incorporated into retro and adeno viral vectors. Studies in several laboratories have however indicated that, although in vitro expression can be obtained, in vivo production has not been seen. Internal DNA sequences with the ΔB F VIII cDNA appear to repress expression. If the expression problems can be resolved then it is likely that ΔB F VIII will be effective, therapeutically since preliminary studies with a commercial ΔB F VIII recombinant product (F VIII SQ, Pharmacia) are encouraging.

In view of the smaller size of F IX cDNA, most studies on gene therapy for haemophilia have used the F IX model, with a F IX cDNA of 2.8 kb incorporated into a retroviral vector or adenovirus vector. Prior to 1993 all such studies involved ex vivo transduction using retroviral vectors containing the complete F IX cDNA. The transferred F IX genes have been expressed in a variety of cells, including rabbit hepatocytes, canine skin fibroblasts, rat endothelial cells, and human fibroblasts. Although functionally normal F IX was produced in vitro, in vivo production has been less than expected and often only transient [44]. This is related to the cell type and vector used.

It is encouraging to note that considerable progress is being made, and that a large number of gene therapy research groups are working specifically in the area of haemophilia gene therapy. However, major problems still must be overcome, particularly in relation to vector design, gene delivery systems and level of gene expression. Safety and ethical considerations must also be addressed. However, as noted by Peake [45], the cost benefits of a single or infrequent treatment resulting in haemostatic levels of F VIII or F IX would have enormous impact on haemophilia care worldwide.

9.2 Recommendations

Although recognizing that significant progress has been made towards the goal of gene therapy for haemophilia, it should be understood that major developments are

necessary in vector design and levels of gene expression before gene therapy becomes a clinical reality. However, once available, gene therapy will have a major impact on haemophilia care both in the developed and developing world. The continuing active support of WHO and WFH through education and the dissemination of information is recommended.

10. LIST OF PARTICIPANTS

Dr Erik Berntorp, Department of Coagulation Disorders, Allmanna Sjukhuset, S-214012 Malmo, Sweden

Dr Doreen B. Brettler, Worcester Memorial Hospital, 119 Belmont Street, Worcester, MA 01606, USA

Dr Mammen Chandy, Hematology Department, Christian Medical College Hospital, Vellore 632004, Tamilnadu, India

Dr Peter Jones, Haemophilia Centre, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-upon-Tyne NE1 4LP, UK

Dr Christine Lee, Haemophilia Centre and Haemostasis Unit, Royal Free Hospital, London NW3 2QG, UK

Dr Jeanne M. Lusher, Department of Pediatrics, Wayne State University, School of Medicine, and Division of Haematology-Oncology, Children's Hospital of Michigan, Detroit, Michigan 48201, USA **(Rapporteur)**

Professor Ian Peake, Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

Dr Kevin Rickard, Royal Prince Alfred Hospital, Missenden Road, Camperdown, Sydney, N.S.W. 2050, Australia

Dr Stephanie Seremetis, Department of Medicine, Mount Sinai School of Medicine, Box 1078, New York, NY 10029, USA

WFH SECRETARIAT

Professor Pier Mannucci, A. Bianchi Bonomi Hemophilia and Thrombosis Centre, 9 via Pace, I-20122 Milan, Italy **(Chairman)**

WHO SECRETARIAT

Dr E.N. Chigan, Director, Division of Noncommunicable Diseases, WHO, Geneva, Switzerland

Dr Victor Boulyjenkov, Responsible Officer, Hereditary Diseases Programme, Division of Noncommunicable Diseases (**Secretary**), WHO, Geneva, Switzerland

Miss P. Corcoran, Global Blood Safety Initiative, Health Laboratory Technology and Blood Safety Unit, Programme on Health Technology, WHO, Geneva, Switzerland

Dr A. Wasunna, for Programme Manager, Programme on Health Technology, WHO, Geneva, Switzerland

11. REFERENCES

1. Nilsson IM, Berntorp E, Löfqvist T, Petterson H. Twenty-five years experience of prophylactic treatment in severe hemophilia A and B. J Intern Med, 232:25-32, 1992.

2. National Hemophilia Foundation. Medical and Scientific Advisory Council (MASAC) recommendations concerning prophylaxis. Medical Bulletin No. 193, Chapter Advisory No. 197, 1994. The National Hemophilia Foundation, New York, N.Y.

3. Carlsson M, Berntorp E, Bjorkman S, Lindvall K. Pharmacokinetic dosing in prophylactic treatment of hemophilia A. Eur J Haematol 31:247-252, 1993.

4. Watson HG, Ludlam CA, Rebus S, Zhang L, Peutherer JF, Simmonds P. Use of several second generation serological assays to determine the true prevalence of hepatitis C virus infection in haemophiliacs treated with non-virus inactivated factor VIII and IX concentrates. Br J Haematol 80:514-518, 1992.

5. Kasper CK, Lusher JM and the Transfusion Practices Committee, AABB. Recent evolution of clotting factor concentrates for hemophilia A and B. Transfusion 33:422-434, 1993.

6. Mannucci PM. Clinical evaluation of viral safety of coagulation factor VIII and IX concentrates. Vox Sang 64:197-203, 1993.

7. Peerlinck K, Vermylen J. Acute hepatitis in patients with haemophilia A. Lancet 341:179, 1993.

8. Mannucci PM, Gdovin S, Gringeri A, Colombo M, Mele A, Schinaia N, et al. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. Ann Intern Med 120:1-7, 1994.

9. Williams MD, Cohen B, Beddal AC, Pasi K, Mortimer PP, Hill FGH. Transmission of parvovirus B19 by coagulation factor concentrates. Vox Sang 58:177-81, 1990.

10. Lefrére J-J, Mariotti M, Thauvin M. B19 parvovirus DNA in solvent-detergent treated anti-haemophilia concentrates. Lancet 343:211-212, 1994.

11. Guillaume T. Parvovirus B19 and blood products. Lancet 343:1101, 1994.

12. Kurtzman G, Ozawa K, Cohen B, Hanson G, Oseas R, Young NS. Chronic bone marrow failure due to persistent B19 parvovirus infection. N Engl J Med 317:287-294, 1987.

13. Centers for Disease Control. Risks associated with human parvovirus B19 infection. Morb Mort Wkly Rep 38:81-97, 1989.

14. Lusher JM. Thrombogenicity associated with factor IX complex concentrates. Semin Hematol 28:3-5, 1991.

15. deBiasi R, Rocino A, Miraglia E, Mastrullo L, Quirino AA. The impact of a very high purity Factor VIII concentrate on the immune system of human immunodeficiency virus-infected hemophiliacs: A randomized prospective, two year comparison with an intermediate purity concentrates. Blood 78:1918-22, 1991.

16. Seremetis S, Aledort L, Bergman G, Bona R, Bray G, Brettler D, et al. Three year randomized study of high purity *vs.* intermediate purity factor VIII concentrates in symptom-free HIV-seropositive haemophiliacs: Effects on immune status. Lancet 342:700-703, 1993.

17. Nilsson IM, Lethagen S. Current status of DDAVP formulations and their use. In: Lusher JM, Kessler CM (eds). Hemophilia and von Willebrand's Disease in the 1990s. Amsterdam: Excerpta Medica Int Congr Series 943:443-453, 1991.

18. Lusher JM. Myocardial infarction and stroke: is the risk increased by desmopressin? In: Mariani G, Mannucci PM, Cattaneo M (eds). Desmopressin in Bleeding Disorders. NATO ASI Series A: Life Sciences. New York: Plenum Press 42:347-353, 1993.

19. Morfini M, Messori A, Cinotti S, Rafanelli D, Filimberti E, Boni E, et al. Comparative studies on available clotting factor concentrates. In: Lusher JM, Kessler CM (eds). Hemophilia and Von Willebrand's Disease in the 1990s. Amsterdam: Excerpta Medica Int Congr Series 943:213-218, 1991.

20. Rickard KA. Guidelines for therapy and optimal dosages of coagulation factors for treatment of bleeding and surgery in haemophilia. Haemophilia 1995, vol. 1, Suppl. 1, pp:8-13.

21. Martinowitz U, Shulman S, Gitel S, Horozowoski H, Heim M, Varon D. Adjusted dose continuous infusion of factor VIII in patients with haemophilia A. Br J Haematol 82:729-734, 1992.

22. Lusher JM, Arkin S, Abildgaard CF, Schwartz RS and Kogenate Previously Untreated Study Group. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. N Engl J Med 328:453-459, 1993.

23. Bray GL, Gomperts E, Courter S, Gruppo R, Gordon EM, Manco-Johnson M, et al. A multicenter study of recombinant factor VIII (Recombinate): safety, efficacy and inhibitor risk in previously untreated patients with hemophilia A. Blood 83:2428-2435, 1994.

24. Ehrenforth S, Kreuz W, Scharrer I, Linde R, Funk M, Gungor T, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet 339:594-598, 1992.

25. Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermylen J. A higher than expected incidence of factor VIII inhibitors in multitransfused hemophilia A patient treated with

intermediate purity pasteurized factor VIII concentrate. Thromb Haemostas 69:115-118, 1993.

26. Kasper CK. Laboratory tests for factor VIII inhibitors, their variation, significance and interpretation. Blood Coag & Fibrinolysis 2:7-10, 1991.

27. Kernoff PBA. The clinical use of porcine factor VIII. In: Kasper CK ed. Recent Advances in Hemophilia Care. Alan R. Liss, Inc., New York, pp:47-56, 1990.

28. Brettler, DB, Forsberg AD, Levine PH, Aledort LM, Hilgartner MW, Kasper CK et al. The use of porcine factor VIII concentrate in the treatment of patients with inhibitor antibodies to factor VIII:C. A multicentre USA experience. Arch Intern Med 149:1381-1385, 1989.

29. Hedner U, Feldstedt M, Glazer S. Recombinant F VIIa in hemophilia treatment. In: Lusher JM, Kessler CM (eds). Hemophilia and von Willebrand's disease in the 1990s. Amsterdam: Excerpta Medica Int Congr Series 943:283-292, 1991.

30. Nilsson IM, Berntorp E. Induction of immune tolerance in hemophiliacs with inhibitors by combined treatment with IVIG, cyclophosphamide and factor VIII or IX. In: Kasper CK (ed). Recent Advances in Hemophilia Care. Alan R Liss Inc, New York, pp:69-78, 1990.

31. Sultan Y, White GC, Aronstam A, Bosser C, Brackmann HH, Brochier G et al. Hemophilic patients with an inhibitor to factor VIII treated with high dose factor VIII concentrate. Nouv. Rev Fr Hematol 28:85-89, 1986.

32. Mariani G. Immune tolerance to factor VIII. International registry data. In: Aledort L, Hoyer L, Lusher J, Reisner H, White GC (eds). Inhibitors to Coagulation Factors. Plenum Publ., New York, 1994 (in press).

33. Klein JP, Bailly E, Schneweis KE, Brackmann H-H, Hammerstein U, Hanfland P, et al. Acute HIV-1 infection in patients with hemophilia B treated with B-propiolactone-UV-inactivated clotting factor. Thromb Haemostas 64:336-337, 1990.

34. Decker CF, Masur H. Current status of prophylaxis for opportunistic infections in HIV-infected patients. AIDS 8:11, 1994.

35. Lee CA. Management of patients with HIV and/or hepatitis. Haemophilia 1995, vol. 1, Suppl. 1, pp:26-34.

36. Lusher JM, Kessler CM, Laurian Y, Pierce G. Viral contamination of blood products. Lancet 344:405-406, 1994.

37. Rizetto M. Hepatitis delta: the virus and the disease. J Hepatol 1:S145, 1990.

38. Troisi CL, Hollinger FB, Hoots WK, Contant C, Gill JC, Ragni M et al. A multicenter study of viral hepatitis in a United States hemophilia population. Blood 81:412-418, 1993.

39. Davis GL. Interferon treatment of chronic hepatitis. Am J Med 96(suppl.1A):41S-51S, 1994.

40. Takahashi M, Yamada G, Miyamot R, Doi T, Endo H, Tsuji T. Natural course of chronic hepatitis C. Am J Gastroenterol 88:240-243, 1993.

41. Chandy M. Management of hemophilia in developing countries with available resources. Haemophilia 1995, vol. 1, Suppl. 1, pp:44-48.

42. Jones P. Living with Haemophilia. Philadelphia, F.A. Davis Co., 1974.

43. Jones P. Haemophilia: A Global Challenge. Haemophilia 1995, vol. 1, pp:11-13.

44. Hoeben RC, Valerio D, van der Eb AJ,, van Ormondt H. Gene therapy for human inherited disorders: techniques and status. Crit Rev Oncol/Haematol 13:33-54, 1992.

45. Peake I. The role of gene therapy in haemophilia. Haemophilia 1995, vol. 1, Suppl. 1, pp:40-43.

* * * * *