
Reviews / Analyses

Modern treatment of haemophilia*

E. Berntorp,¹ V. Boulyjenkov,² D. Brettler,³ M. Chandy,⁴ P. Jones,⁵ C. Lee,⁶
J. Lusher,⁷ P. Mannucci,⁸ I. Peak,⁹ K. Rickard,¹⁰ & S. Seremetis¹¹

Many rapid advances have been made in the diagnosis and therapy of haemophilia. Nevertheless, the condition still poses problems and challenges (e.g., joint disease, transfusion-transmitted diseases, inhibitors, provision of care in developing countries, and education and cost issues). WHO and the World Federation of Hemophilia held a joint meeting in Geneva, on 21–23 March 1994, to discuss and review current and future approaches to the management of haemophilia and its complications, including prospects for genetic technology and gene therapy in developed and developing countries. The present review article summarizes the discussions and recommendations made by the participants.

* Based on the report of a joint WHO/World Federation of Hemophilia meeting on the Control of haemophilia: modern treatment of haemophilia, Geneva, 21–23 March 1994 (Unpublished document WHO/HDP/WFH/94.6, 1994). Other relevant reports include the following: *Report of a joint WHO/WFH meeting on the possibilities for the prevention and control of haemophilia, Geneva, 26–28 March 1990* (Unpublished document WHO/HDP/WFH/90.3); and *Report of a joint WHO/WFH meeting on the control of haemophilia: carrier detection and prenatal diagnosis, Geneva, 10–12 February 1992* (Unpublished document WHO/HDP/WFH/92.4). Single copies of these reports are available from the Hereditary Diseases Programme, Division of Noncommunicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

¹ Department of Coagulation Disorders, Allmänna Sjukhuset, Malmö, Sweden.

² Hereditary Diseases Programme, Division of Noncommunicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this address.

³ Worcester Memorial Hospital, Worcester, MA, USA.

⁴ Hematology Department, Christian Medical College Hospital, Vellore, Tamilnadu, India.

⁵ Haemophilia Centre, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-upon-Tyne, England.

⁶ Haemophilia Centre and Haemostasis Unit, Royal Free Hospital, London, England.

⁷ Department of Pediatrics, Wayne State University, School of Medicine, Detroit, MI, USA.

⁸ A. Bianchi Bonomi Hemophilia and Thrombosis Centre, Milan, Italy.

⁹ Department of Medicine and Pharmacology, Royal Hallamshire Hospital, Sheffield, England.

¹⁰ Royal Prince Alfred Hospital, Missenden Road, Camperdown, Sydney, Australia.

¹¹ Department of Medicine, Mount Sinai School of Medicine, New York, USA.

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Primary prophylaxis in haemophilia care

Although many persons with haemophilia who received blood products over the period 1979–84 have died of acquired immunodeficiency syndrome (AIDS), many are still alive but have human immunodeficiency virus (HIV) infection and declining cellular immunity, with or without AIDS-defining illness. Many of these individuals are also positive for hepatitis C virus (HCV) antibodies. There is no cure for either of these bloodborne viral illnesses; finding more effective modes of treatment therefore remains a necessity.

Fortunately, with only a few exceptions, there have been no reports of new cases of HIV infection resulting from transfusion of blood or clotting factor concentrates for several years. Thus more attention can be focused on other problems and questions caused by haemophilia, e.g., the advantages and disadvantages of prophylaxis in the prevention of joint disease, the 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 persons with haemophilia who live in developing countries can best be managed with the available resources.

Rationale and experience to date

What is the role of primary prophylaxis in haemophilia care? In Sweden, the prevention of joint and musculoskeletal disease in severe haemophiliacs has

been accomplished by starting prophylaxis early in life (age, 1–2 years), with dosages and dosage intervals aimed at keeping factor (F) VIII or F IX trough levels >1%. The rationale behind this approach is that persons with trough levels >1% F VIII or F IX have far fewer bleeding episodes and a much milder clinical course than those with severe haemophilia (trough levels <1% F VIII or F IX).

While several groups of investigators have reported small series of patients utilizing various prophylactic regimens, the most comprehensive study to date was carried out in Malmo, Sweden; Nilsson et al. have published 25-years' experience with prophylaxis involving 60 patients with severe haemophilia A and B (1). Over the 25-year study period the 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, the most recent subset of 15 boys (now aged 4–12 years), who began prophylaxis at 1–2 years of age, have experienced no episodes of joint bleeding and have excellent orthopaedic and radiological joint scores (all zero) (1).

The situation 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) recommended that in the USA 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). MASAC also recommended that a mechanism be developed to evaluate periodically joint status, to document any complications, and to record all costs associated with each child's prophylaxis. A further recommendation was that the risks versus the benefits and all possible problems associated with prophylaxis be discussed with each family, including venous access problems and complications that could result from indwelling central venous catheters (2).

Also, based mainly on the excellent results in Sweden, the Canadian Hemophilia Society recommended in May 1993 that prophylactic treatment be offered to all young children with severe haemophilia.

Cost versus benefits

Although there has been concern that primary prophylaxis may be considerably more costly than episodic ("on demand") treatment, this is not necessarily the case. For example, Carlsson et al. investigated the use of individual pharmacokinetics as an aid to determining the optimal dosage of F VIII for each patient, with emphasis on the impact of different dosage regimens on cost. Their findings indicated

that use of kinetic principles to determine the dose of F VIII can be more cost-effective (3) and that prevention of joint bleeding and haemophilic arthropathy should result in much less time lost from school or work, fewer costly emergency room visits, fewer hospitalizations, less need for orthopaedic interventions, and enhanced patient self-esteem. It is to be hoped that centres beginning primary prophylaxis programmes (or controlled studies of primary prophylaxis versus episodic treatment) will incorporate prospectively well-designed cost-benefit analyses so that the overall relative costs of primary prophylaxis versus "on demand" treatment can be determined.

Recommendations

- Since the main goal is to prevent joint bleeding and its sequelae, prophylaxis should be considered as optimal management for persons with severe haemophilia A and B (baseline level <1% F VIII or F IX). Treatment should be started at 1–2 years of age and be continued indefinitely.
- Where prophylaxis is not feasible or appropriate, "on demand" therapy should be given as early as possible upon onset of a bleeding episode.

Viral safety of currently available products

Donor screening and virucidal methods

Although clotting factor concentrates are still produced from plasma collected from blood 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 plasma donors and the availability of a variety of viral attenuation methods have resulted in safer plasma-derived F VIII and F IX concentrates. Mandatory donor screening for HIV-1 and HIV-2, and tests for seropositivity to HCV (4) and hepatitis B surface antigen (HBsAg) have greatly reduced the viral burden of the 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. The methodologies used 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 *n*-heptane or with hot vapour under high pressure, or by adding a detergent/solvent mixture during manufacture (5, 6).

Viral safety and continued transmission of certain viruses

Although for some of the currently available concentrates viral safety studies have been carried out on haemophilic patients who had no previous exposure to blood products, for others no such studies have been made. For the latter concentrates, inferences can only be drawn from studies of another product treated using a closely similar virucidal methodology. Additionally, although published studies of viral infections involving patients not enrolled in prospective viral safety studies may be more difficult to evaluate (in terms of cause and effect), their results can still be useful. For example, recent reports of viral hepatitis A among 85 European haemophiliacs (from Belgium, Germany, Ireland and Italy) who had received a solvent/detergent-treated F VIII concentrate clearly indicate that such treatment cannot inactivate non-lipid enveloped viruses (7, 8). Also, another non-enveloped virus, human parvovirus B 19, has infected a number of persons with haemophilia who had been infused with concentrates that were pasteurized, vapour-treated, or solvent/detergent-treated (6, 9–11). None of the current virucidal methods therefore seem to be effective against parvovirus B19, which can cause serious complications such as bone marrow failure and chronic anaemia in immunocompromized individuals and hydrops fetalis in pregnant women (6, 12, 13).

Protection against bloodborne viruses

Other pathogenic viruses with features similar to HAV and human parvovirus B 19 may exist that can enter the blood supply. It was unanimously agreed at the meeting that the goal of absolute safety should not be abandoned. 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 vaccinating them against viral hepatitis A and B, rigorous donor selection and screening, and seroconversion surveillance programmes aimed at detecting any product that may be transmitting a bloodborne virus.

Because 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.

Role of recombinant clotting concentrates

Where they are available and affordable, recombinant (r) F VIII concentrates are preferable to human-

plasma-derived products, because of their added margin of viral safety. Recombinant F VIII has been used in humans since 1987 and to date, both commercially available products (Kogenate™, Miles, Berkeley, CA, USA; and Recombinate™, Baxter, Glendale, CA, USA) have had an excellent track record of safety. A third rF VIII concentrate (rF VIII-SQ, Kabi Pharmacia, Stockholm, Sweden) has been undergoing prelicensing clinical trial in Europe since March 1993. Although the *theoretical* risk of transmission of other viruses that might be associated with mammalian cell cultures, bovine albumin or murine monoclonal antibodies should be borne in mind, rF VIII appears to offer not only viral safety, efficacy, and a very low incidence of minor side-effects, but also the possibility of an unlimited supply.

Currently, there are no available rF IX concentrates; however, at least one rF IX concentrate (produced by Genetics Institute, Cambridge, MA, USA), is being developed.

Recommendations

- Plasma-derived coagulation F VIII concentrates, treated using currently available virucidal methods, carry a low risk of transmitting HIV, HBV, and HCV.
- Manufacturers of blood products should develop virucidal methods to inactivate bloodborne viruses that are resistant to current virucidal methods.
- The viral safety of clotting factor concentrates for use in haemophilia B is less well established.
- Continued surveillance of the viral safety of all products (both plasma-derived and recombinant) is needed.

Products for treating or preventing bleeding in persons with haemophilia A or B

Types of products

Although it is certainly not true worldwide, in many countries there are now several types of relevant products to choose from. Such products can be plasma-derived or recombinant, are subjected to various types of viral attenuation procedures, and differ in purity. The choice of a particular product is generally influenced by its perceived viral safety, efficacy, availability, purity, cost, and ease of handling (storage, mixing and administration). Assuming that the full array of products is available, and that all are equally effective, viral safety and cost are 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 HBV and HBC; however, they can transmit other bloodborne viruses such as human parvovirus B19. Although currently produced virally attenuated plasma-derived concentrates appear to be reasonably safe, rF VIII provides an extra margin of viral safety and thus is preferable if it is affordable. At present, no licensed rF IX products are available (although at least one is being developed).

Product considerations for haemophilia B

For persons with haemophilia B another safety issue to be considered is thrombogenicity (5, 14). F IX complex concentrates (prothrombin complex concentrates (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 injuries or large intramuscular haemorrhages, in those with significant hepatocellular disease, and in neonates. Under such circumstances, one of the high-purity, "coagulation F IX concentrates" should be used rather than PCCs. While considerably more expensive than PCCs, the high-purity F IX products can be quite cost-effective if their use avoids thromboembolic complications.

Product purity considerations

What about product purity? While purer would seem to be better, is there evidence to support this, especially in view of the higher costs of so-called ultra-pure products? During the purification processes used (e.g., immunoaffinity purification of plasma-derived F VIII and F IX concentrates), several log-units of virus are lost; thus, whatever viral attenuation process is used, there is less viral contamination of the starting material. Additionally, several studies have shown that cellular immunity is better preserved in HIV-seropositive individuals who are treated with immunoaffinity-purified F VIII concentrates than with intermediate purity F VIII concentrates (15, 16).

Use of 1-deamino-8-D-arginine vasopressin

For persons with mild or moderate haemophilia A, 1-deamino-8-D-arginine vasopressin (DDAVP) is the treatment of choice. This synthetic agent effects a rapid 2–10-fold (average, 3-fold) increase in the level of F VIII (and von Willebrand factor) and is available in several formulations. Although DDAVP is generally given intravenously (dose, 0.3 µg/kg) for surgical procedures or other in-hospital uses, the highly concentrated nasal spray formulation is ideal for use in the home. Side-effects are uncommon as

long as certain precautions are observed. It must be borne in mind that because DDAVP is a potent anti-diuretic agent, hyponatraemia and water intoxication may occur (17, 18).

Recommendations

- For persons with haemophilia A, viral safety should be the primary criterion for choosing between available products.
- For persons who are HIV-seropositive, the use of immunoaffinity-purified and recombinant F VIII concentrates is recommended.
- For persons with mild or moderate haemophilia A, DDAVP should be used whenever appropriate.
- 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.

Optimal dosages of products

Guidelines

Perhaps surprisingly, there is no consensus concerning the optimal dosage of F VIII or F IX for treatment (or prevention) of the various types of bleeding that can occur in persons with haemophilia, i.e., what dosage is sufficient to control bleeding without being excessive. Published formulae can be used to calculate the dosage necessary to achieve a given level of F VIII or F IX in the recipient, and published determinations of the biological half-lives of infused F VIII and F IX can be used to determine dosage intervals. Although these calculated values are not absolute, and may vary slightly from patient to patient and perhaps also from product to product (19), they are useful guidelines.

In contrast, 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). It can reasonably be assumed that smaller dosages will be required if a contained haemorrhage (e.g., acute haemarthrosis, iliopsoas haemorrhage) 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 resting the affected part and use of an antifibrinolytic agent for invasive dentistry or other bleeding in the oral cavity are, of course, also extremely important.

Surgery

For surgical procedures on individuals with haemophilia, it is essential that there is appropriate communication and planning between the medical staff, the surgeon, and the 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 administered by continuous infusion (20, 21); this will not only prevent dangerously low trough levels caused by delays in infusing follow-up doses, but will often result in the use of less clotting factor and enable the level of F VIII or F IX to be monitored at any time.

Recommendations

For the haemostatic management of the person with haemophilia, an accurate assessment of the level of F VIII or F IX is essential.

- Episodes of bleeding in haemophilia patients require F VIII or F IX replacement therapy. This therapy must be safe, administered promptly, and continued for a sufficient duration to control fully the bleeding episode.
- Surgery involving patients with 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.

Management of haemophiliacs with inhibitors

Extent of the 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 (F VIII level, <1%), the majority early in life after relatively few days' exposure to F VIII. In each of three 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 days' exposure. In addition to age and severity of haemophilia, other patient risk factors for inhibitor development include type of gene defect (e.g., 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).

Detection and quantification of inhibitors

Centres that are evaluating and treating persons with haemophilia must have the capability to detect and quantify inhibitors. Laboratory screening can be performed 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).

Low and high responders

Although patients who form inhibitor antibodies in low concentration only, i.e., <5 Bethesda units (so-called "low responders"), can generally be managed using normal or slightly increased doses of F VIII, those who produce inhibitor antibodies in higher concentrations usually cannot. Such individuals are particularly difficult to manage.

Therapeutic options for high responders. Therapeutic options for treating bleeding episodes in high responder inhibitor patients include the following: high dose, human or recombinant F VIII concentrates, sometimes given by infusion; F IX complex concentrates (PCCs), either standard or purposely activated PCCs (APCCs); porcine F VIII; or the investigational agent, rF VIIa (Novo Seven™, Novo-Nordisk, Gentofte, Denmark). Usually, a PCC or APCC at a dose of 75 units per kg is used as first-line treatment for bleeding episodes, although these products are not as effective as F VIII for noninhibitor patients and cannot be relied upon to prevent or control bleeding. Other disadvantages of PCCs and APCCs, *inter alia*, are that their precise mechanisms(s) of action are unknown, there are no laboratory parameters for determining their effectiveness, and large, repetitive doses may be hazardous. 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, Wales), can be quite effective in patients whose inhibitors have little or no cross-reactivity with porcine F VIII (27, 28). Its advantages include a high rate of success in controlling or preventing bleeding in properly selected patients, and that the recipient's F VIII response can be measured and followed. Since it is a foreign species protein, the disadvantages of using Hyate: C include the risk of allergic re-

actions, rarely anaphylaxis. Allergic reactions can be minimized or prevented by premedicating the recipient with 100 mg of intravenous hydrocortisone. Although Hyate:C is being used for home treatment in selected patients in the United Kingdom, its use is mainly reserved for surgical procedures or in the hospital management of more serious bleeding episodes.

Although not yet licensed for use, Novo SevenTM (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). The biological half-life of rF VIIa is short (2–4 hours); thus repeat doses, if necessary, must be given every 2–3 hours (29). This product has not yet been evaluated for home treatment. Thus, whether or not it will prove to be more effective than PCCs or APCCs for early treatment of acute haemarthrosis is not known at present.

Immune tolerance regimens

Because of the limitations of available treatment modalities for bleeding in inhibitor patients, there has been considerable interest in attempts 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 tested in infants and children as well as adults with F VIII or F IX inhibitors. Many of the current ITI regimens use F VIII alone, generally starting with large daily doses of F VIII. However, some groups (e.g., in the Netherlands) have induced tolerance with much lower doses of F VIII; others use a combination of 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 prophylaxis (regularly scheduled infusions) in order to maintain suppression of their inhibitor antibody. None the less, it is noteworthy that in a multicentre study of patients with induced immune tolerance several years previously, Sultan et al. found that 8 of the 18 patients still had undetectable or very low levels of inhibitor and no anamnestic responses to infused F VIII (31). On behalf of the International Society on Thrombosis and Haemostasis F VIII and F IX Subcommittee, Mariani & 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 et al. in the USA have developed a randomized, controlled trial aimed at comparing responses to daily doses of F VIII alone versus F VIII plus a short course of IVIG and cyclophosphamide.

Other ongoing studies are aimed at elucidating the underlying immune mechanisms involved in inhibitor antibody development, disappearance, and induction of immune tolerance. A further 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 a family history of high titre inhibitors).

Recommendations

- 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 access.
- For patients with inhibitors the benefits and risks of elective surgery should be carefully considered. Surgery should only be performed in a comprehensive haemophilia centre and only after consultation and planning between the surgeon and appropriate members of the haemophilia team.

Management of patients with HIV infection and/or hepatitis

Extent of the problem: HIV and AIDS

It is estimated that approximately 8500 individuals in the USA became infected with HIV via clotting factor concentrates between 1978 and 1984; at least 4000 of these individuals have developed AIDS. With the exception of a small outbreak of cases reported in 1990 (33), no new cases of seroconversion among recipients of clotting factor concentrates have been reported in North America or Europe since 1986. However, in some parts of the world where nonvirally attenuated products are still being used, new HIV infections are no doubt still occurring.

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. Although there is still no cure for HIV infection, as study data accrue the recommendations for treatment change. At the moment it appears that drug combinations are likely to be more effective than single agents; combinations

of various drugs with zidovudine produce a more sustained reduction in HIV viral load and a more sustained increase in CD4 counts.

Prophylaxis is important in the prevention of opportunistic infections such as *Pneumocystis carinii* pneumonia, toxoplasmosis, *Mycobacterium avium* complex, as well as fungal infections (34), and can certainly improve patients' quality of life. However, those managing HIV-infected individuals must keep themselves up to date on the current recommendations about 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 also important. Proper handling of needles, syringes, blood and body fluids can prevent secondary cases, as can education and counselling on the sexual transmission of HIV. In the USA estimates indicate that 10–15% of regular sexual partners of HIV-infected haemophiliacs have become infected with the virus, as have a number of infants born to HIV-infected mothers.

Viral hepatitis

Hepatitis A, B, C and D viruses have all been transmitted by blood products to various extents. Although HAV does not produce a chronic infection, recently reported outbreaks of viral hepatitis A resulting from solvent/detergent-treated clotting factor concentrates highlight the fact that certain bloodborne viruses (non-lipid coated viruses such as HAV and human parvovirus B19) are not killed by currently used viral attenuation methods (6–11, 36). Vaccines are available and are recommended for prevention of HAV and HBV infection (although an HAV vaccine is not yet licensed for use in the USA); only those persons who are persistently positive to HBsAg are susceptible to HDV infection (37).

Although serological tests for screening blood and plasma donors for HBsAg have been available since the 1970s (5), an antibody test for HCV became available only in 1990 (4, 5). Subsequently, several studies of North American and European haemophilic populations have 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, experience ongoing viral replication that can progress to chronic hepatitis. Some will develop end-stage liver disease or hepatocellular carcinoma many years later (3, 40). Individuals responsible for treating haemophiliacs who are HCV seropositive have to decide if and when to intervene with liver biopsy and/or interferon alpha (39), and what to tell patients and their families about the prognosis and expected response to

treatment. Although interferon often results in improvements in liver pathology and liver enzyme levels, the beneficial effects may be short-lived once therapy is stopped. For the person who is doubly infected with HIV and HCV, the likelihood of progression to liver failure is greater (20-fold greater) than that with HCV infection alone (35); this may well reflect increased HCV replication as a result of the immunosuppressive effects of HIV infection.

Recommendations

- Individuals with haemophilia and their sexual partners should be tested for HIV-1, HBV, and HCV.
- Vaccination against HBV should be given to susceptible individuals.
- 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.

Management of haemophilia in developing countries

Extent of the problem

Management of haemophilia in developing countries presents formidable challenges. Government and family monetary resources are usually inadequate, knowledge and awareness about haemophilia and its management often nonexistent, with often no access to proper diagnostic testing, and therapeutic material is inadequate — not only in quantity but in terms of its viral safety. While there are variations in populations with regard to income, education, and motivation levels, estimates indicate that less than 5% of the population in developing countries would be able to provide a level of treatment for a haemophiliac son like that available in developed countries (41).

Need for education. Provision of education on haemophilia is of the utmost importance. There must be greater awareness about the condition and its management, not only among health care workers, but among patients and their families. As noted by Jones (42), patient and family education remains the single most important weapon against haemophilia and its complications. The World Federation of Hemophilia (WFH), through its national member organizations, should take an active lead in this area, by developing educational programmes, literature and audiovisual materials that are culturally, socioeconomically and linguistically appropriate.

Need for regional reference centres. There should be regional reference centres with experienced and knowledgeable health care professionals who can coordinate haemophilia services. Such reference centres should have diagnostic laboratory capabilities, staff trained in the evaluation and medical and surgical care of persons with haemophilia, and a modern and well-equipped blood bank that can prepare and store FFP and cryoprecipitate. Regional reference centres 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 (e.g., solvent/detergent treatment of plasma and heat treatment of cryoprecipitates). Manufacturers and other relevant bodies in developed countries should help by making available virally attenuated clotting factor concentrates through WFH and WHO—it is encouraging to see that this has begun to happen as a result of one action of WFH's Decade Plan (43).

Countries with sufficient infrastructure and resources should be encouraged and given the technical help to produce recombinant F VIII. Although it could be argued that this is not realistic at present, the goal of providing adequate amounts of a safe product to all persons with haemophilia should not be abandoned. Recombinant technology not only provides an added margin of viral safety, but the possibility of an unlimited supply.

In the meantime, while therapeutic materials remain scarce and are often unattainable, families and health care providers should be instructed in the use of supportive measures for joint and muscle bleeding, e.g., application of ice packs and use of appropriate analgesics.

Recommendations

- Developing countries should set up coagulation reference centres in tertiary medical facilities to coordinate services for patients with haemophilia and other disorders of haemostasis.
- Haemophilia services should be integrated with the existing health care infrastructure (41).
- 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.
- Since self-sufficiency for coagulation factors through blood donation will take time to achieve, and in view of viral safety issues, developing coun-

tries with the necessary infrastructure should explore the possibility of producing recombinant coagulation factors.

Gene therapy

Technological advances and problems to be solved

In stark contrast to the current status of haemophilia care in developing countries, rapid technological advances in recent years have led to the development of 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 the accurate carrier detection and antenatal diagnosis of haemophilia.

The cloning of the F VIII and F IX genes and their expression in mammalian cells has raised 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, in theory, 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 haemophilia.

Although the full F VIII DNA sequence is too large (8.8 kilobases (kb)) to be incorporated into retroviral and adenoviral vectors, and thus cannot be efficiently transduced by these vectors, cDNA with most of the B encoding domain deleted (Δ B F VIII ca. 5.7 kb in length) can be incorporated into retro- and adenoviral vectors. Studies in several laboratories have indicated, however, that, although *in-vitro* expression can be achieved, *in-vivo* production remains elusive. Internal DNA sequences with the Δ B F VIII will be effective therapeutically since preliminary studies with a commercial Δ B F VIII recombinant product (F VIII SQ, Pharmacia, Stockholm, Sweden) are encouraging.

Because F IX cDNA is smaller, 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 with 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.

Considerable progress has already been made, and a large number of research groups are working specifically on 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. None the less, as noted by Peake (45), the cost-benefits of a single or infrequent treatment that produced haemostatic levels of F VIII or F IX would have enormous impact on haemophilia care worldwide.

Recommendations

- Although significant progress has been made, major breakthroughs in vector design and levels of gene expression are needed before gene therapy for haemophilia becomes a clinical reality. However, once available, such therapy will have a major impact on haemophilia care in both developed and developing countries.
- The continuing active support of WHO and WFH through education and the dissemination of information is recommended.

Résumé

Traitement moderne de l'hémophilie

De grands progrès ont été réalisés dans de nombreux domaines touchant au diagnostic et au traitement de l'hémophilie; toutefois, il reste encore des problèmes à résoudre et des défis à relever en ce qui concerne les complications articulaires, les maladies transfusionnelles, les inhibiteurs, le traitement de l'hémophilie dans les pays en développement, l'éducation et le coût des traitements. L'OMS et la Fédération mondiale de l'hémophilie (WFH) ont tenu une réunion conjointe à Genève du 21 au 23 mars 1994 pour analyser et passer en revue les questions relatives à la prise en charge actuelle et future de l'hémophilie et de ses complications, y compris les possibilités offertes par les techniques génétiques et la thérapie génique, tant dans les pays développés que dans les pays en développement. Après une étude approfondie de chaque sujet, le groupe a élaboré une série de recommandations qui sont résumées ci-après.

Etant donné que l'objectif principal est de prévenir l'hémarthrose et ses séquelles, la prophylaxie doit être considérée comme la méthode de prise en charge optimale pour les personnes atteintes d'hémophilie A ou B grave (niveau de base des facteurs VIII ou IX $>1\%$). Le traitement doit être entrepris à l'âge de 1-2 ans et poursuivi

indéfiniment. Lorsque la prophylaxie n'est pas possible ou indiquée, un traitement "à la demande" doit être institué aussitôt que possible, dès que survient une hémorragie.

Pour les hémophiles A, le principal critère de choix entre les différents produits disponibles doit être la sécurité virale. Lorsqu'on utilise les concentrés de facteur VIII de coagulation dérivé du plasma et soumis aux procédés virucides actuels, le risque de transmission des virus de l'immunodéficience humaine (VIH), de l'hépatite B (VHB) et de l'hépatite C (VHC) est faible. Pour les patients VIH positifs, il est recommandé d'employer des concentrés de facteur VIII purifiés par immunoaffinité ou obtenus par génie génétique. Pour l'hémophilie A légère ou modérée, la 1-déamino-8-D-arginine vasopressive (DDAVP) est le traitement de choix. En ce qui concerne l'hémophilie B, des concentrés de facteur IX hautement purifiés doivent être utilisés lorsqu'il existe un risque élevé de complications thrombotiques. Dans toutes les autres situations, on peut également envisager l'utilisation de concentrés du complexe de prothrombine. Les tests de recherche des virus VIH-1, VHB et VHC doivent être pratiqués sur les hémophiles et leurs partenaires sexuels. Dans un contexte de soins complets, la surveillance de ces maladies virales transmises par transfusion doit être assurée par des analyses de laboratoire et des examens cliniques réguliers. Les patients doivent recevoir un traitement prophylactique et antiviral approprié.

Le traitement des hémorragies, nécessite le remplacement des facteurs VIII et IX. Ce traitement doit être sûr, administré promptement et poursuivi jusqu'à ce que l'hémorragie soit parfaitement maîtrisée. Les interventions chirurgicales ne doivent être entreprises qu'après exclusion d'un inhibiteur éventuel. Le diagnostic et le traitement des inhibiteurs doivent être entrepris dans des centres possédant des moyens de laboratoire suffisants et les produits sanguins nécessaires. Lorsque la présence d'un inhibiteur a été diagnostiquée, l'induction d'une tolérance immunitaire doit être envisagée dès que possible. Chez les enfants, cela peut nécessiter la mise en place d'un cathéter veineux central. En présence d'un inhibiteur, les avantages et les risques d'une intervention chirurgicale non urgente doivent être soigneusement pesés. De telles interventions ne doivent être entreprises que dans un centre spécialisé bien équipé et elles doivent être soigneusement planifiées après consultation entre le chirurgien et le personnel soignant.

Bien que des progrès significatifs aient été faits sur la voie de la thérapie génique de l'hémo-

philie, il reste encore beaucoup à faire dans le domaine de la conception des vecteurs et du degré d'expression génique avant que cette forme de traitement ne devienne une réalité clinique. Cependant, lorsqu'elle sera opérationnelle, la thérapie génique modifiera profondément le traitement de l'hémophilie tant dans les pays développés que dans le monde en développement. Il est recommandé que l'OMS et la WFH poursuivent leurs efforts dans les domaines de l'éducation et de la diffusion de l'information.

Pour la prise en charge de l'hémophilie, les pays en développement devraient établir des centres de référence de coagulation pour les questions dans les établissements médicaux tertiaires afin de coordonner les services aux patients atteints d'hémophilie et d'autres troubles de l'hémostase. Les services d'hémophilie devraient être intégrés dans l'infrastructure actuelle des soins de santé. Un modèle pouvant être modifié selon les besoins de chaque pays est suggéré. Etant donné qu'il faudra encore longtemps pour atteindre l'auto-suffisance en facteurs de coagulation obtenus à partir des dons de sang, et compte tenu des problèmes de sécurité virale, les pays en développement qui possèdent l'infrastructure nécessaire devraient envisager la possibilité de produire des facteurs de coagulation par génie génétique.

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