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I16 Hemophilia

P.M. Mannucci*. *Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Medicine and Medical Specialties, IRCCS Maggiore Hospital and University of Milan, Italy*

In the last few decades, the management of patients with hemophilia has witnessed dramatic improvements, through the large availability of safe plasma-derived and recombinant products for replacement therapy. Another important step forward is related to the larger and larger implementation of primary prophylaxis in children and of secondary prophylaxis in adults who have chronic synovitis and recurrent bleeding. Currently the main problem in patients with hemophilia is the onset of antibodies inactivating the infused clotting factor (inhibitors), even though the advent of immune tolerance regimens, capable to eradicated inhibitors, and the availability of products that bypass the intrinsic coagulation defects has improved the management of these patients. Cure of hemophilia through gene transfer is being attempted, but it is relatively far from being implemented on a large scale.

Keywords: Hemophilia A; Factor VIII inhibitors – recombinant factors immunotolerance

The last two decades of the second millennium have witnessed dramatic improvements in the management of patients with inherited factor VIII (FVIII) and IX (FIX) deficiency (the hemophilias) [1]. There are also excellent weapons for the treatment of von Willebrand disease, the inherited bleeding disorder due to the deficiencies of the multimeric glycoprotein von Willebrand factor [2]. The current situation is much less satisfactory for recessively inherited coagulation disorders, that are still mainly treated with fresh-frozen plasma or cryoprecipitate (the latter employed for afibrinogenemia and factor XIII deficiency) [3].

Plasma factors: The current high degree of safety of plasma-derived FVIII and FIX concentrates stems from the adoption of methods meant to detect the presence of viruses in source plasma and to inactivate those that may have escaped screening (virucidal methods such as pasteurization, dry-heating at high temperatures, solvent/detergent, nanofiltration) [1]. The only currently perceived threat is that the abnormal prion that causes the new variant of Creutzfeldt-Jakob disease might be transmitted by blood products [4], although the plasma fractionation process seems to be able to remove large amounts of prions. Other emerging infectious agents, such as the coronavirus causing SARS, the West Nile virus and that causing avian influenza are not considered impending risks for transfusion in patients with hemophilia, because viremia is transient and current virucidal methods should be able to inactivate them. Since the early 1990s, no case of transmission of viral infections such as hepatitis and HIV has been documented in patients with hemophilia [1].

Recombinant factors: Availability of these products for the treatment of hemophilias has further increased the safety of replacement therapy. Efficacy and safety were clearly shown in prospective studies carried out in the early 1990s, both in previously treated and untreated patients, and by post licensure experience [5–8]. The first generation products had come in contact with human- and animal-derived proteins during manufacturing and formulation. Concern about the use of human- and animal-derived proteins has led to their elimination in the manufacturing process, so that now there are a few recombinant FVIII and FIX that are manufactured without contact with such proteins and are not stabilized with human albumin in the final formulation.

Targets for the improvement of recombinant FVIII are to increase stability and availability; to enhance the expression and specific activity of the molecule; to render it less immunogenic and less neoantigenic by removing and replacing the domains that trigger more frequently inhibitor development; and to slow FVIII plasma clearance, in order to increase the time intervals between doses in the setting of prophylaxis [9]. The latter strategy seems at the moment the most advanced towards clinical use. For hemophilia B patients, there are plans to produce large amount of this protein from the milk of transgenic pigs (the so called bioreactor).

Patients with inhibitors: Treatments that bypass the defects in FVIII or IX in intrinsic coagulation have dramatically improved the management of these patients, who previously had a high rate of musculoskeletal abnormalities and even of death due to uncontrollable bleeding [1]. Steps forward have been the availability of plasma-derived bypassing fractions containing activated and non-activated forms of FII, FIX and FX in controlled amounts [1], and, more recently, a recombinant preparation of activated factor VII [10]. Even though the success rate of these preparations in the control of bleeding is somewhat lower than the 80–90% success rate obtained with recombinant FVIII and FIX in hemophiliacs without inhibitors, clinical situations that were previously poorly

handled, including elective surgical procedures, can now be successfully carried out using these products [1]. It is also possible to clear inhibitors with protocols of immune tolerance that involve the continued administration of large doses of FVIII until inhibitors are no longer detected and patients respond again to FVIII [1].

Gene transfer: At least 5 trials of gene transfer in hemophilia A and B started in the last few years [11]. Early results were encouraging, because measurable levels of FVIII or FIX were obtained in most of the 40 patients enrolled in phase I-II clinical trials. None of these patients developed inhibitors against factors produced by transfected genes. The limits of these early studies were short and limited expression of the transgene, so that the plasma factor levels were too low and transiently detectable to truly improve the clinical picture. Other problems were host immunological reactions to some vectors, transient presence of the transgene in the seminal fluid of recipients and the observation of insertional mutagenesis in patients with SCID treated with retroviral vectors [11]. It must be borne in mind that currently available treatments of hemophilia are safe and efficacious, so that monogenic diseases other than hemophilia should perhaps be preferred as early models for gene transfer (muscular dystrophy, cystic fibrosis SCID).

Conclusions: The treatment of hemophilia has dramatically improved since the 1970s, when concentrates of FVIII and FIX have made possible home treatment and regular prophylaxis. Unfortunately this dramatic progress in treatment, that led to an increase of life expectancy and quality of life in these patients, was dramatically halted in the 1980s by the epidemics of HIV infection and hepatitis. These problems were tackled efficiently and rapidly, so that progress took off again in the 1990s, with the availability of safe concentrates (both recombinant and plasma derived). The beginning of the third millennium has witnessed the advent of gene therapy, that however has not yet led to the cure of hemophilia that patients eagerly await. Currently FVIII inhibitors remain the most important unresolved problem, even though life expectancy and quality of life of these patients have improved. An unresolved issue is whether or not products for replacement therapy that contain only FVIII (typically, recombinant products) are more liable to trigger the onset of inhibitor in previously untreated hemophiliacs that products that in addition to FVIII contain also von Willebrand factor (typically, most plasma derived products) [12–14].

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Correspondence to: P.M. Mannucci, MD. Via Pace 9, 20122 Milan, Italy.
Tel: +39 02 55035421; fax: +39 02 50320723.
E-mail address: pmmannucci@libero.it

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