

TREATMENT OF HEMOPHILIA: THE PRESENT AND THE FUTURE

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The last two decades of the last millennium have witnessed dramatic improvements in the management of patients with inherited factor VIII (FVIII) and IX (FIX) deficiency (the hemophilias). The current situation is much less satisfactory for recessively inherited coagulation disorders, that are still mainly managed with fresh-frozen plasma or cryoprecipitate (the latter employed for afibrinogenemia and factor XIII deficiency).

Plasma factors. The current safety of FVIII and FIX concentrates stems from the progressive adoption of methods meant both to decrease viral load in source plasma and to inactivate viruses that may have escaped screening (virucidal methods such as pasteurization, dry-heating at high temperatures, solvent/detergent, nanofiltration). The only currently perceived threat is that the abnormal prion that causes new variant Creutzfeldt-Jakob disease might be transmitted by blood transfusion, although the plasma fractionation process seems to be able to clear large amounts of abnormal prions. Other emerging infectious agents, such as the coronavirus causing SARS or the West Nile virus, are not considered an impending risk, because viremia is transient and current virucidal methods should be able to inactivate them.

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 '90s, both in previously treated and untreated patients, and by post licensure experience. The first generation

preparations came in contact with human- and animal-derived proteins during manufacturing and formulation. Concern about use of human- and animal-derived raw materials has led to their elimination in the manufacturing of these products, so that now there are recombinant FVIII and FIX manufactured without contact with such proteins and not stabilized with human albumin.

Future developments. 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 strongest and more frequent domains that trigger inhibitor development; and to slow its plasma clearance, in order to increase the time intervals between doses in the setting of continuous prophylaxis. For hemophilia B patients, there are advanced 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 a high risk of death due to uncontrollable bleeding. Steps forward have been the availability of plasma-derived bypassing fractions containing activated forms of FIX and FX in "controlled" amounts, and, more recently, of a recombinant preparation of activated factor VII. Even though the success rate of these preparations is somewhat lower than the 90%-95% success rate obtained with recombinant FVIII and FIX in hemophilias

without inhibitors, clinical situations that were previously poorly handled, including elective surgical procedures, can be managed with these products.

Gene transfer. At least 5 trials of gene transfer in hemophilia A and B started in the last 5-6 years. Early results were encouraging, because measurable levels of FVIII or FIX were obtained in the plasma of approximately 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 are short and limited expression of the transgene, so that plasma factor levels were too low and transiently detectable to truly improve the clinical picture of patients. Other problems are host immunological reactions to some vectors, transient presence of the transgene in the seminal fluid of some patients and the observation of insertional mutagenesis in patients with SCID treated with retroviral vectors. It must be borne in mind that currently available treatments of hemophilia are safe and efficacious, so that monogenic and complex diseases other than hemophilia should perhaps be preferred as early models for gene transfer (cancer, muscular dystrophy, SCID etc).