Gene Therapy for Hemophilia

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KEYWORDS

• Gene therapy • Hemophilia • Clinical trials • Adeno-associated virus (AAV) vectors

KEY POINTS

- The best currently available treatments for hemophilia A and B (factor VIII or factor IX deficiency, respectively) require frequent intravenous infusion of highly expensive proteins that have short half-lives.
- Most hemophiliacs worldwide do not have access to even this level of care. In stark contrast, gene therapy holds out the hope of a cure by inducing continuous endogenous expression of factor VIII or factor IX following transfer of a functional gene to replace the hemophilic patient's own defective gene.
- Hemophilia may be considered a "low hanging fruit" for gene therapy because a small increment in blood factor levels (>2% of normal) significantly improves the bleeding tendency from severe to moderate, eliminating most spontaneous bleeds.
- In this review, the authors discuss the data from their own study – the first successful clinical gene transfer in hemophilia B, and results that are now emerging from many similar studies in both hemophilia A and B.

INTRODUCTION

The commonest severe inherited bleeding disorder in all ethnic groups worldwide is hemophilia A, followed by hemophilia B. These are X-linked recessive disorders that result from mutations in the genes for blood clotting factor VIII (FVIII) in hemophilia A or factor IX (FIX) in hemophilia B. The incidence of hemophilia A in live male births is approximately 1 in 5000, and of hemophilia B, 1 in 25,000. Bleeding tendency varies but correlates best with the residual circulating factor level, which in turn depends on

Due to word limits, only essential references are included.

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Hematol Oncol Clin N Am 31 (2017) 853–868
http://dx.doi.org/10.1016/j.hoc.2017.06.011 **hemonc.theclinics.com**
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the genotype of the mutation that prevents synthesis and/or interferes with function of the affected factor. If the residual factor level is 5% of normal or greater, subjects can be assigned to the mild hemophilia category, in which spontaneous bleeding is absent and only occurs after significant trauma. Wherein residual factor level is less than 5% but greater than 1%, patients are considered to have moderate hemophilia with a variable bleeding tendency; some in this group seldom have any bleeding, whereas others experience frequent bleeding after minor trauma. About half of patients with hemophilia A or B have factor levels less than 1% of normal.[1] These individuals have a severe bleeding tendency with frequent spontaneous musculoskeletal and soft tissue bleeding. A recent careful study of the hemophilic patient population at a large Dutch clinic[2] confirmed these correlations and the basic division into severe, moderate, and mild, but added the insight that those mildly affected patients whose residual factor level is 13% or greater never experienced joint bleeding. Thus, factor levels of greater than 13% could be considered as a target for gene therapy to attain. Among those patients who do bleed into their joints, the ankles are most commonly affected starting in early childhood, with knees and elbows affected later. Repeated episodes of intra-articular bleeding cause severe, progressive, destructive arthropathy with deformity leading to complete loss of joint function and attendant disability.

In the absence of replacement therapy, the life expectancy of a boy with severe hemophilia is only about 10 years. This severe shortening of life still applies in many less-developed countries. Even in developed countries until the 1960s, treatment of hemophilia was limited to infusion of fresh frozen plasma. In 1968, the first widely available concentrate for hemophilia A, cryoprecipitate, was introduced.[3] During the 1970s and 1980s, many multidonor factor concentrates were developed to improve the purity, potency, stability, and convenience of administration of factor replacement therapy. However, these developments, depending as they did on large donor pools of often commercially sourced plasma, permitted transmission of human immunodeficiency virus (HIV) and hepatitis C virus. Almost a whole generation of hemophiliacs who were given the new products became HIV positive and died of AIDS before highly effective antiretroviral therapies were developed. During the period 1970 to 1986, every treated patient was also exposed to hepatitis C, and up to 25 years later, some are still succumbing to chronic liver failure resulting from continued infection. From 1986 onward, heat treatment and then the solvent detergent method inactivated both HIV and hepatitis C virus. Since then, there have been no new cases of transmission of those lipid enveloped viruses. Transmission by blood products of other pathogens resistant to inactivation, such as parvovirus,[3] hepatitis A,[4] and prions (variant Creutzfeldt-Jakob disease[5]), remain a major concern. Recombinant factor concentrates are of course free from blood-borne infections, but their availability has been limited to the most developed countries by very high cost and production constraints. With the expiry of patents on recombinant FVIII and FIX, biosimilars and other variants with enhanced pharmacokinetic or other properties are entering the market, with potential for wider availability than hitherto.

In developed countries, standard hemophilia care for severely affected patients now consists of home-administered prophylaxis with safe concentrates intended to maintain factor level greater than 1% of normal. This is a compromise based on cost and practical considerations, which reduces but does not eliminate bleeding. If started in early childhood after the first joint bleed, arthropathy can be largely prevented.[6] When continued throughout life, prophylaxis leads to near normalization of life expectancy.[7] However, the relatively short half-life of FVIII and FIX in the circulation necessitates frequent intravenous administration of factor concentrates (at least 2–3 times a week), which is demanding and extremely expensive; annualized costs of prophylaxis for an adult equal or exceed £120,000 for patients with hemophilia B. Even with

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