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Perspective

Rationale for Gene Therapy in Treatment of Hemophilia A

Aneesha Kumar*

Department of Genetic Engineering, University of Toronto, Toronto, Canada

DESCRIPTION

Hemophilia A and B are X-linked recessive diseases. These diseases result from mutations in the gene for blood clotting factor VIII (FVIII) and factor IX (FIX) independently. About 1 in 5000 live male births is the prevalence of haemophilia A and 1 in 25 000 live male births is prevalence of and that of hemophilia B. Inclusively, they're among the most common inherited bleeding diseases in the world. These diseases are indistinguishable clinically, with the severity of bleeding symptoms varying according to the residual factor activity in a patient's plasma despite the inheritable and biochemical differences. These individualities have a severe bleeding phenotype conforming of frequent spontaneous musculoskeletal and soft tissue bleeding. Repeated occurrences of intra-articular bleeding cause severe progressive destructive arthropathy, with disfigurement leading to complete loss of joint function and attendant disability. Patients have pronounced bleeding after trauma with moderate hemophilia and may bleed spontaneously, whereas in cases with mild hemophilia, bleeding is generally confined to traumatic events; still, indeed these individualities have an increased threat for death from intracranial bleeding compared with the normal population.

Resembling albumin or Fcγ, newly modified synthetic formulations of FVIII and FIX that are pegylated or fused to proteins with a long half- life. These enhanced the stability profile for FX but have been less impressive for FVIII as a result of the dominant purpose of von Willebrand factor in determining its half- life. BIVV001, a new FVIII fusion protein consisting of a single- chain recombinant FVIIIFc fused to the FVIII- binding D′D3 domains of von Willebrand factor, as well as 2 XTEN linkers, has a raised half- life ≥ 38 hours, raising the prospects of extended protection in hemophilia A patients with biweekly dose. In patients with hemophilia B, extended half- life products allow reduction of injection frequency to once weekly or even once biweekly while maintaining advanced trough levels (FIX > 5), despite the reduction of injection frequency. The use of non-clotting factor products to secure hemostasis in patients with a bleeding diathesis is another major development. For example, a bispecific antibody (emicizumab) with 1 arm binding to FIXa and the other to FX facilitates the conversion of FX into its active form, leading to restoration of hemostasis to a degree analogous to an FVIII level of ~ 15 of normal in hemophilia A patients with or without inhibitors. Emicizumab has attractive pharmacokinetic attributes that allow lower frequent (daily to yearly) subcutaneous administration. Emicizumab is active in plasma all of the time and is associated with micro angiopathy and thrombosis, particularly when used in combination with activated prothrombin complex concentrates unlike FVIII. Other new approaches carry the lowering of endogenous anticoagulants, similar as anti-thrombin or tissue factor pathway inhibitor, with antisense RNA technology (fitusiran) or a monoclonal antibody (e.g., concizumab), independently. These approaches their use may be limited by a threat for thrombogenicity even though they have shown efficaciousness in reducing the rate of bleeding in hemophilia A and B patients, including those with inhibitors.

These new curatives are beginning to change the clinical operation of the hemophilias in countries with developed husbandry by dwindling infusion frequence, therefore perfecting compliance with prophylaxis, offering druthers to asset cases, and easing the route of administration. To date, none of these advances have impacted the standard of care for 80% of the world's hemophilia cases who live in corridor of the world with husbandry in transition or development. These cases have little or no access to factor concentrates and have a reduced life expectation, with veritably many surviving beyond their teenage times.

Gene therapy has great appeal because it offers the capability for a cure through endogenous output of FVIII or FIX following transfer of a normal copy of the different gene despite the widening medicinal choice for the treatment of the hemophilia. Because all of their clinical instantiations are due to the lack of a single protein that circulates in minute amounts in the blood stream the hemophilias have always been considered good candidates for gene therapy. Years of clinical experience and natural history studies show that a small increase in circulating strata of the deficient clotting factor to 5 of normal significantly modifies the bleeding diathesis. Therefore, in comparison with the majority of monogenetic diseases the therapeutic aim for gene therapy of hemophilia is modest. A wide range of FIX or FVIII is anticipated to be advantageous and non-toxic therefore, tight regulation of transgene expression isn't necessary.

Correspondence to: Aneesha Kumar, Department of Genetic Engineering, University of Toronto, Toronto, Canada, E-mail: kane721@gmail.com

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