Prevalence and gene therapy for Hemophilia A & Hemophilia B: A review of clinical benefits

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Abstract:
Hemophilia A and B are rare congenital, recessive X-linked disorders caused by lack or deficiency of clotting factor VIII (FVIII) or IX (FIX), respectively. The severity of the disease depends on the reduction of levels of FVIII or FIX, which are determined by the type of the causative mutation in the genes encoding the factors (F8 and F9, respectively). The hallmark clinical characteristic, especially in untreated severe forms, is bleeding (spontaneous or after trauma) into major joints such as ankles, knees and elbows, which can result in the development of arthropathy. Intracranial bleeds and bleeds into internal organs may be life-threatening. The median life expectancy was ~30 years until the 1960s, but improved understanding of the disorder and development of efficacious therapy based on prophylactic replacement of the missing factor has caused a paradigm shift, and today individuals with hemophilia can look forward to a virtually normal life expectancy and quality of life. Nevertheless, the potential development of inhibitory antibodies to infused factor is still a major hurdle to overcome in a substantial proportion of patients. Finally, gene therapy for both types of hemophilia has progressed remarkably and could soon become a reality.

Keywords: hemophilia A, hemophilia b, gene therapy

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1- Introduction:

Haemophilia A and haemophilia B are congenital disorders caused by deficiency or absence of either of two coagulation proteins, factor VIII (FVIII) for haemophilia A (encoded by F8) and factor IX (FIX) for haemophilia B (encoded by F9). In the past, haemophilia C was known as coagulation factor XI (FXI) deficiency; however, at the present time, only haemophilia A and B are considered to be haemophilia, and all other clotting factor deficiencies are referred to as unusual bleeding diseases. The kind of causal mutation determines the severity level [1]. Haemophilia A is an inherited disease caused by a defect in the gene located on the long arm of the X chromosome, causing a qualitative or quantitative deficiency of coagulation factor VIII [2]. Men who carry a defective copy of the FVIII gene on their X chromosome will pass on a normal Y chromosome to all of their male children and an abnormal X chromosome to all of their female daughters. Their sons will not be affected, and all of their female daughters will be carriers of haemophilia A. This is because chromosome X is linked to the inheritance of the disease. With the exception of extremely rare cases of homozygosis or double heterozygosis, carriers who are female have a 50% chance of passing the condition on to their sons at birth and a 50% chance of having daughters who will also carry the disorder [3]. According to popular reports, the prevalence of haemophilia A is 1 in 10,000 in the general population and 1 in 5,000 in the male population. More accurate figures, however, unequivocally demonstrate the impacts of access to diagnosis, registration, and treatment. The prevalence of haemophilia A was estimated to be 12.8 per 100,000 boys in high-income nations and only 6.6 per 100,000 males in low-income countries in a survey including 106 countries [4]. The UK data clearly shows the impact of better registration and maybe treatment: From 9.3 per 100,000 men at the beginning of the national register in 1974 to 21.6 per 100,000 males in 2006, haemophilia A was more common. Younger patients are overrepresented in many low-income nations due to a lower life expectancy among patients with little or limited access to therapy [5]. Christmas disease, or hemophilia B, is the second most prevalent form of hemophilia. Since Stephen Christmas was the first individual to get a diagnosis of the illness in 1952, the ailment bears his name. In the Russian, German, and Spanish royal dynasties, the condition was pervasive. The most well-known family affected by this illness was that of Queen Victoria of England; thus, it is called the "Royal disease" [6]. A genetic disorder called hemophilia is brought on by a lack of one of the blood's clotting proteins. It could be caused by a flaw in the clotting factor gene. Factor VIII and Factor IX genes are located on the X chromosome. Due to its X-linked recessive inheritance pattern, hemophilia B mostly affects men. afflicted men will have 100% carrier daughters but no afflicted sons. 50% of female carriers will give birth to afflicted boys, and 50% will give birth to carrier daughters. Females may be impacted by Lyonization, which is the inactivation of the other X chromosome, or if they inherited the mutant alleles from both of their parents [7]. Less people have HB than HA. According to an international survey, the prevalence of HA in the population was 17.1 per 100,000 men, but the prevalence of HB was 3.8 males per 100,000; this means that 18% of haemophiliacs had HB. For HA, the incidence, or prevalence, at birth was 4.7 per 100,000 for men and 23.2 per 100,000 for females [8]. Similar symptoms are present in both haemophilia A and haemophilia B, and both diseases are characterised by bleeding, particularly into big joints like the elbows, knees, and ankles (the index joints); this joint bleeding eventually results in severe and incapacitating haemophilic arthropathy. No matter how serious the condition is, but particularly in the severe types, rare, life-threatening haemorrhage (such as brain bleeds and bleeds in other internal organs) can nonetheless happen. While substantial bleeding can happen as a result of trauma and surgery, people with moderate to phenotype. In contrast, severe 3 is characterised by frequent spontaneous bleeds. mild haemophilia tend to have a

milder. Due to the development of effective and safe clotting factor concentrates that may be administered as long-term prophylaxis from early childhood in the more severe cases, the treatment of haemophilia has significantly improved over the past several decades. Before the advent of safe blood products, a significant fraction of haemophiliacs receiving treatment with commercially accessible pooled plasma-derived clotting factor concentrates suffered from blood-transmitted diseases such the hepatitis C virus and HIV infections [9]. Results were significantly improved by the introduction of comprehensive care facilities in the 1970s and the home infusion of replacement factor. However, improvement is gradual in low-resource environments, and the majority of haemophiliacs still lack access to effective care on a worldwide scale. The development of anti-FVIII or anti-FIX antibodies as a result of factor replacement therapy still poses a serious risk to the health of haemophiliacs [10]. The market is seeing the introduction of new, enhanced treatments that show promise for the near future. These medications include non-factor-based haemostatic medicines as well as FVIII and FIX concentrates that have been altered to have superior pharmacokinetics and a longer half-life. On the basis of a number of clinical studies' highly encouraging findings, gene therapy is now a reality [11].

2- Results of recent AAV-based gene therapy trials for haemophilia A and B:

In a study 2020, approved that gene therapy with AAV5-hFVIII-SQ vector in 15 participants with severe hemophilia A who had received a single infusion of AAV5-hFVIII-SQ at various dose levels, resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all participants who had received 4×1013 vg per kilogram or 6×1013 vg per kilogram of the gene therapy [12]. In a study 2017, founded that sustentation of therapeutic expression of factor IX coagulant activity after infusion of a single-stranded adeno-associated viral (AAV) vector consisting of a bioengineered capsid, liver-specific promoter and factor IX Padua (factor IX–R338L) transgene at a dose of 5×1011 vector genomes per kilogram of body weight in 10 men with hemophilia B who had factor IX coagulant activity of 2% or less of the normal value. Laboratory values, bleeding frequency, and consumption of factor IX concentrate were prospectively evaluated after vector infusion and were compared with baseline values. Transgene derived factor IX coagulant activity enabled the termination of baseline prophylaxis and the near elimination of bleeding and factor use [13].

3- Discussion:

Gene therapy is a promising treatment option for hemophilia A and B, which are inherited bleeding disorders caused by mutations in the factor VIII or factor IX genes, respectively. Gene therapy aims to deliver a functional copy of the missing or defective gene to the liver cells, where these clotting factors are normally produced. By doing so, gene therapy can potentially restore the production of the missing clotting factors and prevent or reduce bleeding episodes in patients with hemophilia [14]. There are different types of gene therapy vectors that can be used to deliver the therapeutic genes to the liver cells. One of the most widely used vectors is the adeno-associated virus (AAV), which is a small, non-pathogenic virus that can infect both dividing and non-dividing cells. AAV vectors can be engineered to carry different gene constructs, such as the full-length or truncated versions of the factor VIII or factor IX genes, or novel variants with enhanced activity or reduced immunogenicity [15]. AAV vectors are administered intravenously to patients, and they target the liver cells by binding to specific receptors on their surface. Several clinical trials have been conducted or are ongoing to evaluate the safety and efficacy of AAV-based gene therapy for hemophilia A and B. The results so far

have been encouraging, showing that gene therapy can achieve sustained expression of the therapeutic clotting factors in most patients, leading to significant reduction in bleeding frequency and factor replacement therapy use. Some patients have even reached normal or near-normal factor levels after gene therapy, which is considered a functional cure for hemophilia. Moreover, gene therapy has been generally well tolerated, with no serious adverse events related to the vector or the transgene reported. However, gene therapy for hemophilia also faces some challenges and limitations that need to be addressed before it can be widely available for the hemophilia patient population. One of the main challenges is the immune response against the vector or the transgene, which can reduce the efficacy and durability of gene therapy. Some patients may have pre-existing antibodies against the AAV vector, which can prevent them from receiving gene therapy or reduce its effectiveness. Others may develop antibodies against the vector or the transgene after gene therapy, which can lead to clearance of the transduced liver cells or inhibition of the clotting factor activity. To prevent or manage this immune response, some strategies have been proposed, such as screening patients for AAV antibodies before gene therapy, using different AAV serotypes or capsid variants, administering immunosuppressive drugs such as corticosteroids, or combining gene therapy with immune tolerance induction protocols. Another challenge is the variability in gene therapy outcomes among patients, which may depend on several factors, such as the vector dose, the vector type, the gene construct, the patient's genotype, phenotype, age, weight, liver function, and co-morbidities [16]. Therefore, it is important to optimize the gene therapy regimen for each patient and monitor their factor levels and clinical outcomes over time. Furthermore, it is necessary to evaluate the long-term safety and efficacy of gene therapy for hemophilia, as well as its impact on quality of life and cost-effectiveness. Some potential long-term risks of gene therapy include insertional mutagenesis, oncogenesis, germline transmission, and reactivation of latent viruses. gene therapy for hemophilia is a novel and exciting treatment option that has shown great clinical benefit in several trials. However, there are still some issues that need to be resolved before gene therapy can be widely adopted in clinical practice. More research is needed to improve the safety and efficacy of gene therapy vectors and constructs, to overcome the immune response against gene therapy products, to understand the factors that influence gene therapy outcomes, and to assess the long-term benefits and risks of gene therapy for hemophilia.

4- Conclusion:

Hemophilia A and B are rare bleeding disorders caused by the deficiency or dysfunction of clotting factors VIII and IX, respectively. These factors are essential for the normal blood coagulation process, which prevents excessive bleeding from injuries or internal damage. Patients with hemophilia A and B have a higher risk of bleeding complications, such as hemarthrosis (bleeding into joints), hematoma (bleeding into tissues), and intracranial hemorrhage (bleeding into the brain). Early diagnosis of hemophilia and early management helps in improving the quality of living of the patient and prevents early development of complications. Recent successes of gene therapy for hemophilia indicate the possibility of curing the disease, and will lead to a paradigm shift in its treatment.

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