



Review Article

Hemophilia Gene Therapy: The Dawn Of A New Era In Treatment

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ARTICLE INFO

Published: 08 Nov. 2024

Keywords:

Haemophilia A, valoctogene roxaparvovec, exogenous factor VIII, emicizumab, gene therapy, and adeno-associated viral vector.

DOI:

10.5281/zenodo.14056311

ABSTRACT

Haemophilia is a well-known X-linked genetic disorder that results in insufficient levels of the proteins necessary for blood coagulation cascade. It can be caused by a mutation in the F8 (factor VIII) gene in haemophilia A or the F9 (factor IX) gene in haemophilia B. Factor VIII or factor IX activities in the blood plasma are extremely low in patients with severe haemophilia; they are thought to be less than 1%. Historically, prophylactic or episodic intravenous injection of exogenous factor VIII (FVIII) has been the accepted standard of care for haemophilia A. A therapeutic breakthrough was the creation of emicizumab, a humanized bispecific monoclonal antibody that mimics activated FVIII. Despite being one of the most cutting-edge methods for treating haemophilia, adeno-associated virus (AAV)-based gene therapy still faces difficulties with vector immunogenicity, potency and efficacy, genotoxicity, and persistence. One of the characteristics of haemophilia is a lack of coagulation factors VIII or IX. In order to stop bleeding, regular intravenous recombinant or plasma-derived factor replacement is the mainstay of therapy for severe haemophilia. Although this medication effectively stops bleeding, many find that receiving repeated injections is taxing.

INTRODUCTION

According to the text of the Talmud, haemophilia has been investigated since antiquity, from the papyri of ancient Egypt to the second century AD. Because this was typical in the royal ailment, nineteenth-century scientists called the illness the “kings’ disease.” [1] Rare X-linked inherited bleeding disorders called hemophilia A and B are brought on by deficiencies in coagulation factors VIII and IX, respectively. [2,3] Haemophilia A is thought to affect 12 out of every 100,000 males in

the USA, while haemophilia B affects 3.7 out of every 100,000 males. [4] Haemophilia B is currently treated primarily with bleeding prophylaxis, which entails costly, lifelong infusion therapy using recombinant factor IX or plasma clotting factors. The cost of blood clotting factors to treat a single patient with haemophilia B can exceed USD 450,000 year, and the total cost of treatment can eventually reach USD 20 million or more, even in affluent nations like the USA, Germany, Japan, etc. Mutations in the F8 and F9

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



genes result in reduced or absent production/function of clotting factor VIII (FVIII; haemophilia A) and clotting factor IX (FIX; haemophilia B), respectively. Haemophilia A and B are rare, X-linked inherited bleeding disorders.[5] Given its demonstrated effectiveness, long-term prophylaxis is currently considered the gold standard of care.[6] Regular injections are required because of the terminal half-life of traditional factor replacement. Patients and healthcare systems may find this burdensome and expensive, which could lead to low compliance and globally restricted patient access to therapy.[7,8] PwH undergoing prophylactic non-replacement therapy might still need factor replacement in the event of breakthrough bleeding, trauma, or surgery.[5] The stable expression of coagulation factors for longer than eight years is made possible by modern medications[9] Treatment burden can be decreased with bioengineered extended half-life clotting factors made by fusion techniques and covalent binding to polyethylene glycol (PEG).[10,11]

Gene Therapy for Haemophilia

Haemophilia gene therapy uses adeno-associated viral (AAV) vectors, which are tiny viruses that target the liver and express endogenous factors. AAV vectors are useful due to their non-pathogenic nature. They transduce both dividing and non-dividing cells, but have modest integration rates. They are delivered via intravenous infusion. After a single IV infusion lasting 1-3 hours, the vector particles are absorbed by liver cell receptors and transfer DNA to the cell's nucleus.[12] The AAV serotype 5 (AAV5) is used by both valoctocogene roxaparvovec and etranacogene dezaparvovec-drlb, two gene treatments for haemophilia that target their transgene to hepatocytes using AAV vectors.[13,14] The downside of AAV is that neutralizing antibodies are naturally present in the general population. Can reduce the efficacy of gene

treatments.[15] AAV5 has lower seroprevalence and cross-reactivity compared to other AAVs, which mitigates this potential problem.[16]

Symptoms: The signs and symptoms of haemophilia vary according to your amount of clotting factors. If your clotting factor level is somewhat lowered, you may only bleed after surgery or trauma. If your insufficiency is severe, you may bleed profusely for no apparent cause.

The signs and symptoms of spontaneous bleeding are:

- Unexplained and heavy bleeding from cuts or traumas, especially following surgery or dental procedures.
- Many huge or severe bruises.
- Unusual bleeding following immunizations.
- Joint pain, edema, and tightness
- Blood in the pee or stool
- Nosebleeds without an identifiable etiology
- Infants with inexplicable irritability[16]

Rationale of gene therapy for haemophilia

The treatment of haemophilia has undergone an extensive evolution, effectively translating principles of protein biochemistry and applying molecular biology to enhance patient care.[8] Gene therapy offers a functional version of the gene responsible for the disease, which may be missing or producing a dysfunctional protein. This makes hemophilia an ideal candidate for gene therapy because it is caused by a single gene mutation. The cloning of the F8 and F9 genes resulted in the creation of recombinant clotting factors and sparked gene therapy initiatives aimed at potentially curing the condition.[17] The availability of well-defined mouse and dog models of haemophilia has facilitated extensive preclinical research in gene therapy.[8,18]

The Treatment of Haemophilia Using Blood-Purified Factors VIII and IX

Haemophilia was mostly treated with whole blood plasma transfusions in the 1950s and 1960s. Nevertheless, it lacked the necessary clotting



factors, requiring lengthy infusions of substantial amounts of donor plasma in a hospital environment to ensure that the surgeries yield favorable outcomes. The second half of the 1960s saw the development of cryoprecipitation technology, which made it possible to precipitate the required blood proteins for fresh frozen plasma under a certain thawing regimen. Concentrated clotting factors can be obtained in this way, greatly lowering the infusion volume. When the molecular causes of haemophilia were discovered, the apparent treatment was to extract factors VIII and IX from donor blood and give them to sufferers.

To extract FVIII from plasma, cryoprecipitation was the initial step. This was followed by extraction and precipitation with aluminum hydroxide. Either ion exchange or immunoaffinity chromatography employing monoclonal antibody immobilization is used in the last step of this procedure. Immunoaffinity chromatography produces pure FVIII, while ion exchange chromatography does not eliminate von Willebrand factor (vWF). But the final product is unstable and necessitates serum albumin addition.[19]

Treatment of Haemophilia Using Recombinant Factors VIII and IX

1982 saw the engineering of recombinant FVIII, while 1984 saw the successful cloning of FIX. In the 1990s, the first recombinant protein-based drugs were developed. In 1997, a licensed recombinant FIX drug called BeneFIX was made available to handle haemophilia B.[20, 21] Blood clotting factor preparations are biological medications, thus it's vital to remember that the body could respond negatively to them due to immunological responses. In practical practice, decongestants should be prescribed in place of the medicine if such a case occurs. To choose the best course of treatment, confirmatory immunology testing for IgE should be taken into account. Anaphylactic responses and factor IX inhibitors

may arise in individuals with severe haemophilia who are administered factor IX. In a research involving two individuals with severe haemophilia B who have a skin test, have their RAST factor IX adjusted, and After factor IX desensitization, it was discovered that IgE causes anaphylactic responses. In reaction to the injection of factor IX.[22]. Recombinant factor VIII (rFVIII) preparations were categorized according to the animal or human proteins employed in their manufacture as they were refined over time to lessen immunogenicity.[23] Depending on whether they came from human or animal cell culture during manufacture, recombinant FVIII products can be categorized. The more sophisticated medications use human-derived proteins in a culture medium devoid of albumin, whereas the earlier products used animal proteins in addition to human serum albumin.[24]

Select Phase 3 Gene Therapy Trials

For Haemophilia

1. Valoctogene Roxaparovec GENER8-1 Phase 3 Trial

For Haemophilia A

In 2022, two haemophilia gene treatments were approved for clinical use. In August 2022, the valoctogene roxaparovec received approval in Europe. Dezapar Etranacogene. In the USA, vovec-drlb was approved by the FDA in November. 2022 and February 2023 European approval .[13,14,25] BioMarin Pharmaceutical Inc. created the valoctogene roxaparovec, which is prescribed to treat severe hemophilia A in adult patients who have never had FVIII inhibitors and who do not have measurable antibodies to AAV5. [13] An ongoing, open-label, single-arm trial includes the GENER8-1 Phase 3 clinical trial (NCT03370913) that resulted in this approval. Adult males with severe haemophilia A (FVIII \leq 1 IU/dL) who had been receiving prophylactic FVIII replacement for at least a year before enrollment were included in the study population. Participants

could not have a history of FVIII inhibitors and have received treatment with FVIII concentrates or cryoprecipitate for at least 150 exposure days.[13,26] Those with detectable levels of AAV5 capsid antibodies, significant liver failure, another bleeding disorder, a platelet count less than $100 \times 10^9/L$, or creatinine levels greater than 1.5 mg/dL were not allowed to participate.[13,26] A research change resulted in the exclusion of participants infected with HIV. Following the FDA's advice, The GENE8-1 trial's primary outcome was modified from levels of FVIII activity (using a chromogenic substrate test) to ABR (annualized bleed rate) one year following infusion of the vector AAV5-hFVIII-SQ [26,27]

2.Etranacogene Dezaparvovec-drlb HOPE-B Phase 3 Trial for Haemophilia B

UniQure and CSL Behring developed the gene treatment etranacogene Dezaparvovec-drlb for hemophilia B. AAV5-hFIXco-Padua, an AAV vector-based gene therapy with a hyperfunctional F9 variant, is recommended for the treatment of adult haemophilia B patients who are FIX prophylactic medication users, have experienced life-threatening haemorrhage in the past or present, or have experienced recurrent, severe spontaneous bleeding. There are now 54 participants in the global, open-label, single-arm HOPE-B Phase 3 clinical trial (NCT03569891). Male adults with haemophilia B (defined as FIX activity level ≤ 2 IU/dL) who had severe or moderately severe haemophilia were included in the trial.[14,28] Non-inferiority of the ABR throughout months 7–18 following injection compared with the 26-week lead-in period was the main efficacy endpoint in the HOPE-B trial. The ABR was 4.19 (95% confidence interval (CI) 3.22, 5.45) during the lead-in period, and it dropped to 1.51 (95% CI 0.81, 2.82) over months 7–18, which is consistent with gene therapy's non-inferiority to factor replacement prophylaxis.[28]

3.Comparison of Hemophilia A versus Haemophilia B Gene Therapy

The HOPE-B research for haemophilia B shown that etranacogene deza-parvovec-drlb offers a more sustained response with less side effects than the GENE8-1 study for haemophilia A. hepatotoxicity. While FVIII levels gradually decline following. Therapy with roxaparvovec (valoctocogene) comes from the tranacogene dezaparvovec-drlb phase 2b study results indicated stable high and long-lasting FIX levels three years after treatment. [29]

In other haemophilia B gene therapy trials, recipients of the treatment have maintained their response for almost ten years.[26,30,31] They contemplating therapy must take into account the challenge of estimating expression levels; yet, in the event of little or no response, they may safely return to preventive care.[26,28]

Opportunities Associated with Gene Therapy in Haemophilia A

Gene therapy is a disease-transforming therapy that has the potential to become the new standard for the treatment of individuals with hemophilia A.[32] It may enable the patient to acquire a sustained physiological level of endogenously produced FVIII protein that could provide effective prophylaxis without the requirement for exogenous factor replacement therapy [5,33] Such constant endogenous expression of physiological quantities of FVIII can be expected to eradicate breakthrough bleeding and micro-hemorrhages[32].

Challenges of Gene Therapy in Haemophilia A

The first successful gene therapy report dates back to 2011, when patients with severe haemophilia B underwent intravenous administration of AAV-based liver-directed gene therapy. [34] However, gene therapy targeting haemophilia A has not progressed as quickly as gene therapy targeting haemophilia B. This is primarily because of the



constraints imposed by the size and structure of the FVIII gene, issues obtaining therapeutically high levels of the transgenic protein, and immune responses of cells to the AAV vector capsid. [35] (also found in haemophilia B therapy studies, albeit less so), as well as problems with the length and fluctuation of this type of treatment [3,36,37]

Assessment of Efficacy of FVIII Expression

Trans-gene expression can be directly and easily ascertained through the measurement of FVIII activity. However, normal clinical laboratory assessments of clotting activity differ, with the one-stage test yielding higher levels of FVIII activity than the CSA.[38,39].

In investigations involving liver-directed gene therapy, one-stage assays and/or chromogenic assays have been utilized to quantify the quantities of circulating FVIII or FIX and the length of transgene expression. Comparative investigations for the B-domain-deleted FVIII-SQ in valoctocogene roxaparvovec AAV5-FVIII-SQ revealed a 1.6-fold difference between the values achieved by the two approaches.[39]

Implementing Gene Therapy in a Real-World Setting

Gene therapy is a complicated treatment procedure, and when it is authorized for reimbursement, comprehensive care facilities with substantial experience in treating haemophiliac patients will probably be the first to offer it. To guarantee proper prescription, administration, and monitoring of gene therapy in patients with severe haemophilia, a modified “hub-and-spoke” model with a long-term safety and efficacy surveillance system should be implemented, according to a recent joint publication from the European Association for Haemophilia and Allied Disorders and the European Haemophilia Consortium A [40,41] It is necessary to decide how this treatment service will be set up at the national and local levels, as well as how patients who qualify for gene therapy in Italy will be evaluated, treated, and

managed, given the impending approval of gene therapy for haemophilia A.[42]

II. CONCLUSION

Frequent intravenous injections and the possibility of developing an FVIII inhibitor are part of the current treatment for haemophilia A, which can have a detrimental effect on the quality of life for patients. For individuals with haemophilia A, gene therapy offers the possibility of a single course of treatment. That would permit the impaired FVIII to manifest itself over an extended period of time, with the preservation of steady-state levels of plasma FVIII, reducing bleeding episodes for the recipient’s entire life and lessening the impact of their illness. Since FVIII produced by gene therapy is a physiological protein rather than an exogenous FVIII concentrate or mimicking factor, stable physiological plasma FVIII levels may prevent the decline in joint health. Gene therapy for the management of haemophilia A has now advanced beyond proof of concept, with the realistic anticipation that it may become available to patients in European countries, including Italy, in 2022. [44,45] Since valoctocogene roxaparvovec has the longest term efficacy and safety data (5 years) of any gene therapy now being studied, it is expected to be the first licensed medicine. These findings show that patients who got valoctocogene roxaparvovec had persistent FVIII secretion, which reduced the need for ABR and FVIII replacement treatment. [46] We think that better patient selection and patient expectation management will optimize the advantages of gene therapy. Gene therapy may therefore mark a paradigm change and establish itself as a new gold standard for treating haemophilia A patients, allowing for long-term care and better clinical and patient-centered results, including improved quality of life, for a large number of those affected.

Acknowledgments: The authors would like express to thankful to our Teacher Dr. Salve mam and prof. Ajit B. Tuwar for their Guidance and



support for this review article. Special thanks to Sangale sir for guidance.

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HOW TO CITE: Kanchan Thorat*, Ajit Tuwar, Dr. Megha Salve, Hemophilia Gene Therapy: The Dawn Of A New Era In Treatment, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 11, 467-474. <https://doi.org/10.5281/zenodo.14056311>

