Understanding of Valoctocogene Roxaparvovec (Roctavian) as a Breakthrough Gene Therapy for Hemophilia Type A

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Abstract:

Hemophilia is a hemorrhagic disease characterized by the absence or deficiency of clotting factor VIII (hemophilia A) or clotting factor IX (hemophilia B), and hemophilia C or factor XI deficiency. It affects 1 in 5,000 living males, 1 in 40,000 live males, and 1 in 100,000 live births worldwide (Hemophilia A, B, and C). Emicizumab is a monoclonal antibody that bridges activated factors IX and X to perform the duties of activated factor VIII when it is absent, restoring hemostasis. Intravenous infusion of exogenous FVIII is the current gold standard in hemophilia A treatment. Prophylactic coagulation factor replacement has been shown to reduce arthropathy, decrease the frequency of bleeds, and improve quality of life.

Gene therapy for hemophilia involves targeting hepatocytes, allowing for long-term expression of defective FVIII while maintaining stable plasma FVIII concentrations. The first gene therapy for hemophilia A is Roctavian. Valoctocogene roxaparvovec, the active ingredient in Roctavian, is based on an adeno-associated virus (AAV) that has been altered not to infect people. Roxaparvovec was granted conditional marketing authorization in the EU to treat severe hemophilia A in adults without FVIII inhibitors and AAV5 antibodies.

Keywords: Hemophilia A, Gene Therapy, FIII, Valoctocogene Roxaparvovec (Roctavian), Adeno-Associated Virus (AAV), BioMarin Pharmaceutical Inc.

1. Introduction:

Hemophilia is a hemorrhagic disease characterized by the absence or deficiency of clotting factor VIII (hemophilia A) or clotting factor IX (hemophilia B), and hemophilia C or factor XI deficiency; in 1953, patients who sustained excessive bleeding following tooth extractions were the first to be diagnosed. The estimated prevalence is 1 in 100,000, making it a rare condition.(Castaman et al., 2022)(Jayakrishnan et al., 2019), Hemophilia, an X-linked bleeding disease, results in excessive and frequent bleeding that can be fatal if left untreated (Nienhuis et al., 2017) .

Worldwide hemophilia A affects 1 in 5,000 living males or approximately 85% of all cases; in comparison, hemophilia B affects 1 in 40,000 live males or about 15% of all cases, and hemophilia C affects 1 in 100,000 live births or about 1% of all hemophilia case**s** (Salen & Babiker, 2023) (Iorio et al., 2019)**.**

FVIII is a large protein produced naturally by sinusoidal endothelial cells, particularly in the liver (Castaman et al., 2022). Currently, Factor VIII or factor IX activity levels in plasma are used to categorize the severity of hemophilia: severe if < 1%, moderate if between 1 and 5%, and mild if > 5 and < 40% of normal (ALEDORT et al., 1994). The Project Group advised against changing this classification because it typically correlates well with clinical characteristics. It is acknowledged that this categorization has limitations in that it does not consider the clinical variability in bleeding seen in people with severe hemophilia or between hemophilia A and B (ALEDORT et al., 1994)(Stafford, 2016). The classification of individuals with FVIII levels between 40 and 50% remains unresolved and may need to be addressed in the future (Blanchette et al., 2014)

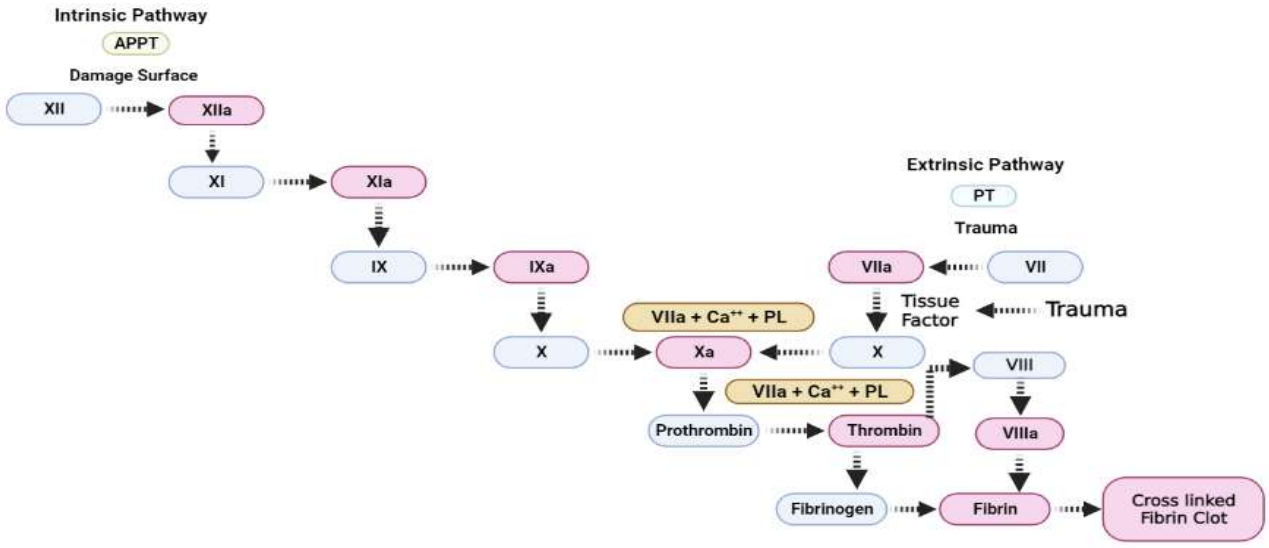

Figure: 1 *Summary of the coagulation cascade, APTT, and PT laboratory measurements represent the intrinsic and extrinsic pathways described in the cascade coagulation model.*

A higher risk of spontaneous and trauma-related bleeding events, including bleeding into the joints that Causes hemophilic arthropathy, exists when endogenous FVIII activity levels are less than 1 IU/dL (1%) in a patient(Castaman et al., 2022). In nations with developed economies, prophylaxis with factor concentrates that aim to keep the factor level >1% of normal is currently the standard of care for patients with severe hemophilia. Regular prophylaxis can substantially avoid arthropathy if it is started in early life.

2. Therapy for hemophilia type A before Roctavian:

The current gold standard in hemophilia A treatment is the intravenous infusion of exogenous FVIII, either as prevention or episodically to treat bleeding events, trauma, or surgical operations(Castaman et al., 2022) Replacement therapy is the preferred form of treatment for hemophilia patients. Prophylactic replacement of the coagulation factor has been demonstrated to reduce arthropathy considerably, decrease the frequency of bleeds, and enhance patients' quality of life in those with severe conditions(Lambert et al., 2018). Emicizumab, a monoclonal antibody with two specificities, bridges activated factors IX and X to perform the duties of activated factor VIII when it is absent and therefore restores hemostasis(Schmitt et al., 2021). Regardless of the presence or lack inhibitors, Emicizumab is delivered subcutaneously. FVIII or by-passing medicines are still necessary for patients with inhibitors for breakthrough bleeds, and surgery and Emicizumab must be given as maintenance therapy (every 7, 14, or 28 days)(Oldenburg et al., 2017) . A novel FVIII fusion protein called BIVV001 consists of a single-chain recombinant FVIIIFc fused to the von Willebrand factor's FVIII-binding D′D3 domains and two XTEN linkers, has a longer half-life of 38 hours, which increases the likelihood that patients with hemophilia A will experience prolonged protection with weekly administration (Konkle et al., 2018). Other innovative methods involve using antisense RNA technology (fitusiran) or a monoclonal antibody (such as concizumab) to reduce endogenous anticoagulants such as antithrombin or tissue factor pathway inhibitor(Sehgal et al., 2015).

These methods have demonstrated effectiveness in lowering the rate of bleeding in hemophilia A and B patients, even those who are using inhibitors. However, their usage may be constrained by a potential for thrombogenicity(Eichler et al., 2018). These novel therapies are beginning to change the clinical management of hemophilia's in countries with developed economies by decreasing infusion frequency, thus improving compliance with prophylaxis, offering alternatives to inhibitor patients, and easing the route of administration. None of these advances have impacted the standard of care for 80% of the world's hemophilia patients who live in parts of the world with economies in transition or development (Ljung, 1999).

3. Hemophilia A Gene Therapy:

Valoctocogene Roxaparvovec:

The first gene therapy for hemophilia A is Roctavian. Valoctocogene roxaparvovec, the active ingredient in Roctavian, is based on an adeno-associated virus (AAV) that has been altered not to infect people (Ozelo et al., 2022). Gene therapy Valoctocogene Roxaparvovec is created by BioMarin Pharmaceutical Inc. to treat hemophilia A. To treat severe hemophilia A [congenital factor VIII (FVIII) deficiency] in adults without a history of FVIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5, (AAV5) valoctocogene roxaparvovec was given conditional marketing authorization in the EU in August 2022(Blair, 2022) .

The virus carries the factor VIII gene; after being administered to a patient as a one-time infusion, it is anticipated that the liver cells would pick up the gene and manufacture the missing factor VIII. This facilitates easier blood clotting and lessens or stops bleeding episodes. The duration of a patient's therapy response to this single infusion is still unknown (Ozelo et al., 2022). The hemophilia A gene transfer techniques that target liver hepatocytes using adeno-associated viral (AAV) vectors are the ones that are most likely to receive regulatory approval. In animal models, lentiviral vectors (LVs) that target hematopoietic stem and progenitor cells ex vivo have demonstrated potential; they integrate into DNA and may potentially cause oncogenesis (Olgasi et al., 2021). The risk that recombination mistakenly recreates a replication-competent and pathogenic virus is another worry with regard to LVVs produced from HIV (Sommer et al., 2012). AAV, a parvovirus family member with a defective replication member, is harmless to people. Recombinant AAV (rAAV) vectors are created by manipulating the vector genome to replace the AAV coding sequences with the desired transgene while using a tissue-specific promoter, as in liver gene therapy (Doshi & Arruda, 2018).

The transgene (or its protein product) must be transported to the physiologically relevant target tissue or tissues expressed stably and not interfere with the functional integrity of the cells in these tissues to treat a hereditary condition with gene therapy (Marchesini et al., 2021).Although liver sinusoid endothelial cells generally produce factor VIII, valoctocogene roxaparvovec targets hepatocytes instead (Arruda, 2015). Creating a treatment that is administered as a single infusion and permits appropriate long-term expression of the defective FVIII while maintaining steady-state plasma FVIII concentrations is the ultimate goal of gene therapy for patients with hemophilia A (Chen et al., 2017).

Valoctocogene roxaparvovec is a recombinant AAV5 vector with codon optimization that expresses the SQ variant of human FVIII with a unique hybrid transcription promoter to the liver (Rangarajan et al., 2017).The non-enveloped icosahedral AAV5 capsid mainly targets the liver while delivering the transgene. A baculovirus-Spodoptera frugiperda (Sf9) insect-cell manufacturing system is used to create the vector itself (Rangarajan et al., 2017). In the 1/2 research (NCT02576795) phase, 15 adults with severe hemophilia A (FVIII 1 IU/dL) received an infusion of valoctocogene roxaparvovec at dosages of $6x10^{12}$ viral genome (VG)/kg (n=1), $2x10^{13}$ VG/kg (n=1), $6x10^{13}$ VG/kg (n=7), or $4x10^{13}$ VG/kg (n=6) (Pasi et al., 2021)). In the $6x10^{13}$ VG/kg and $4x10^{13}$ VG/kg cohorts, respectively, four out of seven and three out of six patients maintained median FVIII levels > 5 IU/dL at 4 and 5 years after treatment (Pasi et al., 2021).

In the phase 3 research (NCT03370913), 134 participants had an injection and followed up for more than 51 weeks. The mean factor VIII activity level among the 132 participants who tested negative for the human immunodeficiency virus increased by 41.9 IU/dl from weeks 49 to 52 (95% confidence interval [CI], 34.1 to 49.7; P0.001; median change, 22.9 IU/dL; interquartile range, 10.9 to 61.3(Ozelo et al., 2022). The mean annualized rates of factor VIII concentrate use and treated bleeding at week 4 had decreased among the 112 participants enrolled in a prospective noninterventional study following infusion by 98.6% and 83.8%, respectively (P0.001 for both comparisons). Every participant experienced at least one adverse event, and 22 out of 134 participants (16.4%) reported severe adverse events. Immunosuppressive medications were used to treat elevated alanine aminotransferase levels in 115 out of 134 patients (85.8%). Headache (38.1%), nausea (37.3%), and increases in aspartate aminotransferase levels (35.1%) were the other most frequent adverse reactions. None of the subjects had thrombosis or the development of factor VIII inhibitors (Ozelo et al., 2022). Factor VIII activity and bleeding prevention remained active and safe for at least two years after the gene transfer (Mahlangu et al., 2023).

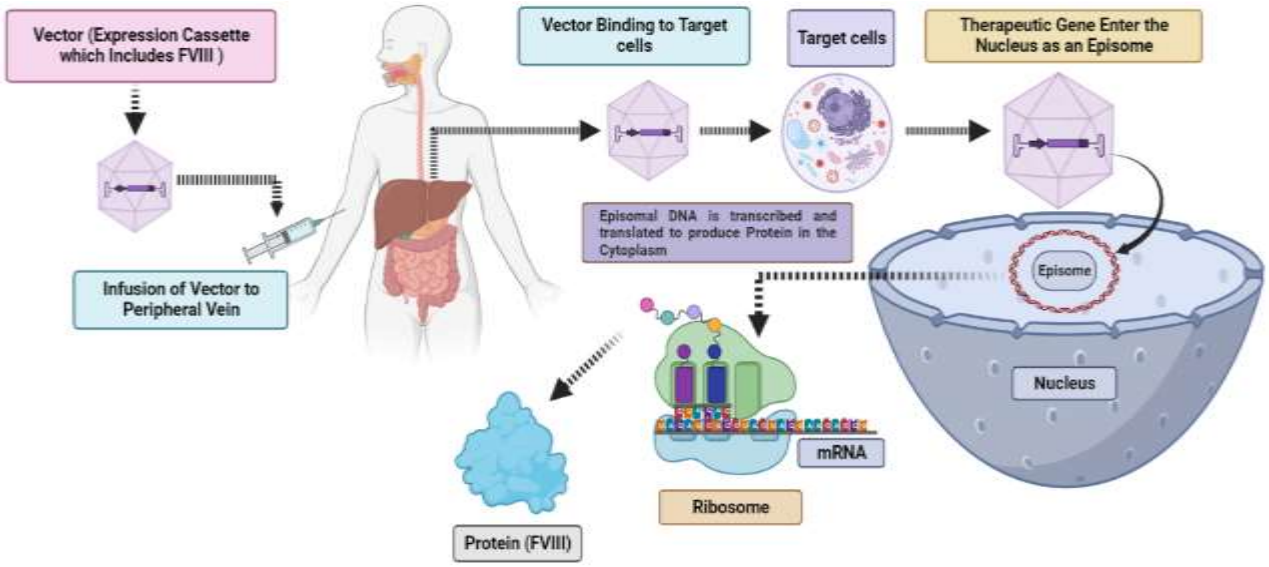

Figure: 2 *is an overview of the gene therapy's adeno-associated viral (AAV) vector-based.*

Additional Hemophilia A Gene Therapy Candidates in the Future:

- **SPK-8016**

Spark Therapeutics is creating the experimental gene treatment SPK-8016 for people with hemophilia A who have inhibitors. It is intended to repair the healthy blood-clotting system in those with the hereditary condition who have failed to respond to replacement therapy.

The effectiveness of SPK-8016 in adult men with clinically severe hemophilia A who have not yet developed FVIII inhibitors and have no AAV-neutralizing antibodies is being examined in phase 1/2, open-label, non-randomized, dose-finding research (NCT03734588) (George et al., 2021). At weeks 3–7, patients received daily oral corticosteroids for 43–38 weeks. Four men who received SPK-8016 at a dose of $5x10^{11}$ vg/kg showed sustained FVIII levels (6.2-21.8%) after 52 weeks, according to preliminary findings. With the proper immunomodulatory regimen, it may be possible to achieve clinically significant FVIII activity with modest vector dosages(George et al., 2021)(Pachakhan et al., 2023).

- **Dirloctocogene Samoparvovec**

AAV3 (specifically, subtype LK03) was used to create the recombinant-AAV vector Dirloctocogene Samoparvovec (SPK-8011), which consists of SPK200, a bioengineered capsid with a liver-specific, truncated transthyretin enhancer and promoter, a synthetic intron sequence, and codon-optimized FVIII cDNA encoding FVIII-S and manufactured with transient triple transfection of human embryonic kidney cells (HEK293 cells) (George et al., 2021).

18 men with hemophilia A participated in phase 1–2 trial (NCT03003533/NCT03432520) and were divided into four dose cohorts; the lowest dose cohort received $5x10^{11}$ vg/kg, and the highest dose cohort received $2x10^{12}$ vg/kg; glucocorticoids were given if an immune response was suspected. Due to a cellular immunological reaction against the anti-AAV capsid resistant to immune suppression, two participants lost all FVIII expression (Castaman et al., 2022)(Sayedi et al., 2022). FVIII expression was still present in the 16 remaining men, 12 of whom had been monitored for more than two years. Following the administration of dirloctocogene samoparvovec, these men's ABR (Auditory Brainstem Response) decreased by 91.5%. Seven trial participants had elevated ALT levels, most of which were minor; one had a grade 2 elevation that necessitated hospitalization for treatment. Four participants reported experiencing glucocorticoid-related adverse effects. The formation of FVIII inhibitory antibodies was not documented in any cases (Castaman et al., 2022). There are also other candidates for hemophilia A gene therapy, such as Giroctocogene Fitelparvovec, TAK-754, BAY 2599023, and AAV8-HLP-hFVIII-V.

Result:

Hemophilia is a hemorrhagic disease characterized by the absence or deficiency of clotting factor VIII (hemophilia A); it affects 1 in 5,000 living males. Emicizumab is a monoclonal antibody that bridges activated factors IX and X to perform the duties of activated factor VIII when it is absent, restoring hemostasis. Gene therapy for hemophilia involves targeting hepatocytes, allowing for long-term expression of defective FVIII while maintaining stable plasma FVIII concentrations.

Valoctocogene roxaparvovec, the active ingredient in Roctavian, is based on an adeno-associated virus (AAV) that has been altered not to infect people. Roxaparvovec was granted conditional marketing authorization in the EU (European Union) to treat severe hemophilia A in adults without FVIII inhibitors and AAV5 antibodies. Valoctocogene roxaparvovec is a recombinant AAV5 vector with codon optimization that expresses the SQ variant of human FVIII with a unique hybrid transcription promoter in the liver.

In the phase 3 research, 134 participants had an injection and were followed up for more than 51 weeks. The mean factor VIII activity level among the 132 participants who tested negative for the human immunodeficiency virus increased by 41.9 IU/dl from weeks 49 to 52 (95% confidence interval [CI], 34.1 to 49.7; P0.001; median change, 22.9 IU/dL; interquartile range, 10.9 to 61.3). The mean annualized rates of factor VIII concentrate use and treated bleeding at week 4 had decreased among the 112 participants enrolled in a prospective noninterventional study following infusion by 98.6% and 83.8%, respectively. None of the subjects had thrombosis or the development of factor VIII inhibitors.

Conclusions:

Hemophilia is a hemorrhagic disease characterized by the absence or deficiency of clotting factor VIII (hemophilia A) or clotting factor IX (hemophilia B), and hemophilia C or factor XI deficiency. Hemophilia A affects 1 in 5,000 living males.

Hemophilia A is currently treated with regular intravenous injections that carry a risk of FVIII inhibitor development and have a poor influence on patient quality of life. With the maintenance of steady-state plasma FVIII concentrations, long-term expression of the defective FVIII is made possible in hemophilia A patients treated with gene therapy, minimizing bleeding episodes over the course of the patient's lifetime and lessening the burden of their disease. Gene therapy for hemophilia involves targeting hepatocytes, allowing for long-term expression of defective FVIII while maintaining stable plasma FVIII concentrations. Valoctocogene roxaparvovec is the first gene therapy for hemophilia A and it's based on an adeno-associated virus (AAV) that has been altered not to infect people. Roxaparvovec was granted conditional marketing authorization in the EU to treat severe hemophilia A in adults without FVIII inhibitors and AAV5 antibodies.

Future Prospective:

Hemophilia is a hemorrhagic disease characterized by the absence or deficiency of clotting factor VIII (hemophilia A). Hemophilia, an X-linked bleeding disease, results in excessive and frequent bleeding that can be fatal if left untreated; it affects 1 in 5,000 living males.

In the phase 3 research, 134 participants had an injection; every participant experienced at least one adverse event, and 22 out of 134 participants (16.4%) reported severe adverse events. Elevated alanine aminotransferase levels were found in 115 out of 134 patients (85.8%). Headache (38.1%), nausea (37.3%), and increases in aspartate aminotransferase levels (35.1%) were the other most frequent adverse reactions. Avoid and decrease the adverse effects of Valoctocogene roxaparvovec. AAV or a gene can be substituted to produce and maintain stable plasma FVIII concentrations for a long time (more than two years) with fewer adverse effects.

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Competing interests: All authors declared no potential personal or financial conflicts of interest.

Ethics statement: This study was ethically approved by the medical bioethics committee of the MIHE ethics committee (code: 1391-1200).

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