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Education

# Advances and challenges with gene therapy for Haemophilia

EDUCATION

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ABSTRACT

**Summary:** Haemophilia is a rare inherited bleeding disorder caused by deficiency in clotting factor that affects around 6,000 people in the UK. Patients with haemophilia require regular prophylactic infusions of the deficient clotting factor intravenously, which causes a large burden on patients and their families. Gene therapy holds promise as a potential cure for Haemophilia. This article critically evaluates the existing evidence for gene therapy in Haemophilia.

**Relevance**: There are several gene therapies in development for inherited conditions such as Haemophilia. Valoctocogene Roxaparvovec, a gene therapy for Haemophilia, is currently being assessed by regulatory authorities worldwide. Medical students and practicing physicians must be aware of the current evidence base for gene therapy for Haemophilia as well as the limitations thereof, to help patients make informed decisions on whether gene therapy is a suitable treatment option for them.

**Take Home Messages:** The current evidence shows that gene therapy is very likely to be effective in increasing clotting factor levels and reducing bleeds for at least 3 years. However, long-term data is limited, and therefore, the durability of the treatment is unknown. Additionally, there is limited evidence on the safety and efficacy of gene therapy in patients with pre-existing antibodies to the viral vector, patients with inhibitors to the clotting factor, and children.

## INTRODUCTION

Haemophilia is a rare bleeding disorder characterised by a deficiency of clotting factors, usually inherited in an X-linked recessive pattern. Haemophilia affects around 6,000 people in the UK. (1) Rarely, Haemophilia can be acquired through spontaneous mutations or the development of antibodies to the clotting factors as part of an autoimmune pathology. (2) There are two main types of Haemophilia: Haemophilia A and B (summarised in Table 1). (3)

| | Haemophilia A | Haemophilia B |
|---|---|---|
| Synonym | Classic Haemophilia | Christmas Disease |
| Mutated Gene | F8 | F9 |
| Deficient Clotting Factor | Factor VIII | Factor IX |
| Incidence | 1 in 5,000 males | 1 in 20,000 males |

**Table 1:** *Types of Haemophilia (3)*

Due to the deficiency of clotting factor VIII or IX, people with Haemophilia cannot form an effective hard fibrin clot on endothelial injury, leading to excessive bleeding. (4) Haemophilia results in prolonged bleeding after injury, haemarthrosis, and in severe cases, spontaneous bleeding that can be life-threatening. (5)
The current standard of care involves replacing the deficient factor VIII or IX through regular infusions. Clotting factors can be given episodically (also called on-demand) or prophylactically. People with mild or moderate Haemophilia rarely experience spontaneous bleeding and therefore are given episodic, or on-demand treatment in direct response to a bleeding episode. Episodic treatment can stop hemorrhage but does not prevent bleeding. (6) Prophylactic therapy is used when a person has moderate or severe Haemophilia and involves regular injections of the deficient clotting factor. Prophylaxis prevents spontaneous bleeding, and therefore, prevents progressive joint deterioration due to joint bleeds. (7)

Despite many advances in developing factor products with longer half-lives, people with Haemophilia still have to visit hospitals 2-4 times a week to receive factor concentrates. This is a huge burden for Haemophilia patients and their carers, affecting their quality of life. The 2018 Chess study showed that people with Haemophilia being treated with prophylaxis had a health utility of 0.87, much lower than the average utility of the general population of 0.93 (a higher score indicates better health). (8) Moreover, there are several barriers to adherence to prophylaxis, including busy lifestyles, dislike of intravenous injection and anxiety about administration. (9) This means despite the availability of factor products, many people still experience bleeds. The limitations of prophylactic therapy means that an alternative, more sustainable treatment is needed for patients with Haemophilia to improve their quality of life.

### Gene therapy for Haemophilia

Gene therapy involves delivering therapeutic genes into target cells or tissue using viral vectors. (10) The goal of gene therapy in Haemophilia is to deliver a normal F8 of F9 gene (which codes for clotting factor VIII and IX, respectively) to the target site. A recombinant viral vector such as the Adeno-Associated Virus (AAV) is used to deliver the gene, to trigger production of the deficient clotting factor. (11) The target site or cells must be non-dividing to ensure durability of gene expression. For this reason, most ongoing clinical trials target liver as the target site. (12)

Haemophilia is an ideal target for gene therapy. The condition is monogenic – it affects only one gene. (13) Trials are easy to conduct because of the easily measurable endpoints such as factor levels and bleeding rates. (14) Most importantly, even a small increase in clotting factor to a level of 1% of normal activity has been shown to lead to reduced bleeding and better quality of life, and therefore, gene therapy does not need to increase factor levels much to have a positive effect on patients' lives. (15)

Gene therapy as a treatment for Haemophilia has been considered for many decades, with the first phase I trial conducted in 1998. (16) The first successful human clinical trial was conducted by Nathwani et al. in 2011 for Haemophilia B, which showed that gene therapy could potentially be a permanent cure for Haemophilia. (17) It also stimulated the influx additional trials which have shown remarkable efficacy.

## EVIDENCE FOR GENE THERAPIES IN HAEMOPHILIA

There are several gene therapies are in late phase development, having shown very promising results in earlier phase trials (summarised in Figure 1). In these trials, gene therapy led to increase in mean factor activity levels from less than 2% at baseline, to between 8% and 70% at various time points after gene therapy. The longest of these four clinical trials, conducted on the gene therapy candidate valoctogene roxaparavovec has showed that factor levels of more than 10% of normal are maintained over a five-year period. The results are very promising for patients with Haemophilia as their quality of life would be significantly improved with the avoidance of regular prophylactic clotting factor infusions and reduced bleeding.

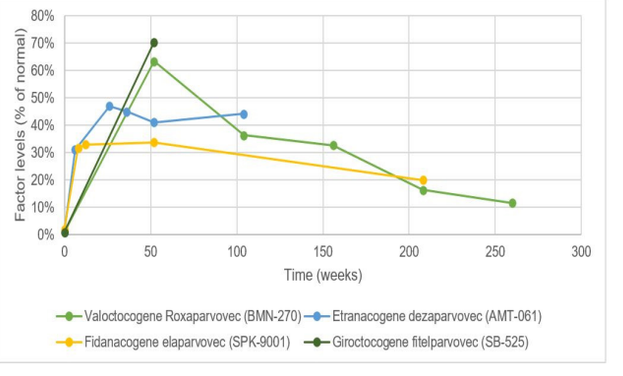


**Figure 1:** *Progression of mean factor levels after various early phase gene therapies in development (18-28)*

The significant increase in clotting factor activity levels has also translated into reduction in mean Annualised Bleeding Rates from pre-treatment levels (summarised in Figure 2). In the clinical trials, patients had 3 to 16.5 annualised bleeding events per year at baseline despite prophylaxis. This decreased to less than one bleed per year on average for most gene therapies, and to an average of

almost 0 bleeds per year for some therapies such as AMT-061.

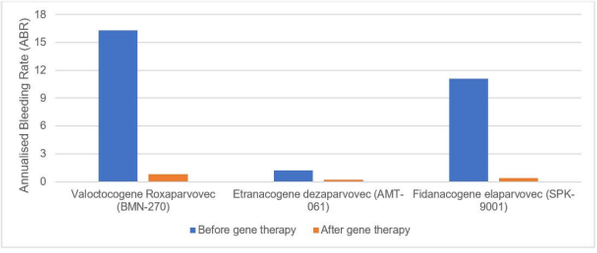


**Figure 2:** *Annualised bleeding rates before and after gene therapy (19, 29, 30)*

These therapies were chosen through identification of ongoing phase 3 trials for gene therapy with published phase 2 trial results.

| Condition | Intervention | Reference |
|---|---|---|
| Haemophilia A | giroctocogene fitelparvovec (SB-525) | 28 |
| Haemophilia A | Valoctogene Roxaparvovec (BMN-270) | 18-20 |
| Haemophilia B | Fidanacogene elaparvovec (SPK-9001) | 24-25, 27, 29 |
| Haemophilia B | Etranacogene dezaparvovev (AMT-061) | 21-23, 26, 30 |

**Table 2:** *Summary of the studies used in the literature review*

These results are very promising for patients with Haemophilia, since gene therapy appears to help in not only avoiding the need for regular clotting factor infusions, but also in improving the efficacy over regular prophylaxis.

## POTENTIAL LIMITATIONS OF GENE THERAPY IN HAEMOPHILIA

Despite the dramatic improvements in efficacy these early phase trials have shown, there are limitations with gene therapy in Haemophilia, which clinicians must be aware of. Gene therapy may not be a viable treatment option in some patient groups with Haemophilia. Even in patients in whom gene therapy has been studied, there are uncertainties about the long-term safety and efficacy of gene therapies. We will discuss some of these key limitations in this section.

**Will factor levels be sustained in the long-term?**
Genomes administered through non-integrating vectors like AAV remain in the cytoplasm of the target cell in episomal form and therefore, cannot replicate during cell division. (31) This means that transgene expression will be lost if the target cells divide, and clotting factor levels may decline over time. Waning clotting factor levels is especially problematic in children because though their blood volume increases, the number of transduced cells remain the same, resulting in a decline in factor activity levels. (32) Current clinical trials of Haemophilia gene therapies confirm that factor activity levels wane over time (see Figure 1), but longer-term follow-up is required to accurately assess the trajectory.
Gene therapy with current vectors cannot, therefore, be seen as a permanent cure. However, research with safe, alternative vectors like lentiviral vectors is ongoing, which could produce sustained transgene expression, potentially offering prospects for a permanent cure. (33)

**Can gene therapy be administered to Haemophilia patients with pre-existing antibodies to the viral vector?**
AAVs are naturally occurring viruses. On exposure to naturally occurring AAV, human immune response causes the development of neutralising antibodies (nAbs) to the virus, which may persist for up to six years after the encounter. nAbs to AAV5 and AAV8, the two commonly used vectors for gene therapy, are prevalent in 25% and 28% of Haemophilia patients from the United Kingdom, respectively. (34) Pre-existing nAbs can prevent the virus from entering the host cell and delivering the therapeutic genome, thereby constituting a major limitation to gene therapy. (35)

The impact of AAV nAbs on efficacy of gene therapy is being tested in late-phase trials for etranacogene dezaparvovec (36) and valoctogene roxaparavovec. Results from the valoctogene roxaparavovec trial has showed that stable Factor IX levels were achieved despite pre-existing nAbs. No correlation was found between pre-existing nAbs and factor levels after gene therapy. (37) While this is extremely promising, most ongoing phase 3 clinical trials of current gene therapies have excluded patients with pre-existing nAbs, which means there would be insufficient evidence on the efficacy of the first generation of gene therapies in people with pre-existing AAV nAbs. (38)

**Can gene therapy be used successfully in people with inhibitors to the clotting factor?**

Most patients with Haemophilia would have been exposed to replacement clotting factors, which are the current mainstay therapy for Haemophilia. Exposure to replacement clotting factors trigger the development of antibodies to the factors. (39) Approximately 30% of people with severe Haemophilia A and in 3-13% in people with severe Haemophilia B develop an inhibitor to the clotting factor, many of them developing inhibitors within a short period of exposure to the deficient factor, and therefore, in childhood. (40)

Currently, the only known treatment for inhibitors is Immune Tolerance Induction (ITI), which involves the administration of high doses of clotting factors to overpower the immune response. If this is successful in removing inhibitors, it will enable patients to also receive gene therapy successfully. (41) However, ITI establishes immune tolerance in only approximately 70% of Haemophilia A patients and 30% of Haemophilia B patients with inhibitors and can potentially lead to serious adverse events. (42)

Very early studies in animal models using alternate vectors such as lentiviruses suggest that gene-therapy could provide transgene expression in sufficiently large quantities to overpower and eradicate pre-existing inhibitors. (43) However, there is limited clinical evidence in humans yet, and once again, current clinical studies exclude patients with inhibitors. (42)

**Can gene therapy be used to treat children with Haemophilia?**
The potential benefits of gene therapy in Haemophilia are particu-

larly prominent in children, especially considering the substantial burden that factor replacement therapy imposes on young children. There are several other benefits to administering gene therapy at a young age. For instance, although nAbs are typically present in neonates because of transmission of maternal antibodies, titers wane over the first year, and remain low until children encounter naturally occurring AAV later in their childhood. (44) Additionally, offering gene therapy early could help prevent the development of clotting factor inhibitors in the first place. (33)

Despite this compelling case for gene therapy to be offered early in life, current trials for Haemophilia gene therapies are not enrolling children, for ethical reasons. There is still limited data about the efficacy, safety and durability of gene therapy in adults, which would make it unethical to begin studying the therapy in children. Until further data is generated, children with Haemophilia may not be eligible for gene therapy.

## CONCLUSION

There have considerable advances in gene therapy for Haemophilia recently and there is promising data to support this. The gene therapies in development have data that confirms that they increase factor levels and reduce bleeding. The first of these therapies is being reviewed by regulators and is likely to be made available soon. However, early data shows that waning of factor levels could be a problem and there is a lack of long-term evidence to show the durability of the treatment. Additionally, gene therapy may not be able to treat everyone with Haemophilia, including people with inhibitors to the clotting factor, people with neutralising antibodies to the viral vector, and children.

Long-term data is needed to accurately determine the durability of gene therapy. Additional research into new vectors, perhaps lentiviral vectors, and conducting trials on a broader group of patients than currently being studied may allow gene therapy to be available for more people with Haemophilia.

Until then, it is important for clinicians to provide clear and balanced information to patients to help them make an informed choice on whether gene therapy could be the appropriate treatment option for them.

Avenues for further research could also include the CRISPR/Cas9 gene editing technology, which has shown promising results in preclinical trials in mice with Haemophilia B. (45)

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