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Is Gene Therapy a Band-Aid or a Cure?

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ABSTRACT

The goal of innovation in treating diseases is to provide a long-lasting solution. For rare diseases such as sickle cell disease (SCD) and hemophilia, this can mean reducing the number of complications or even increasing life expectancy. One of the innovations that is having increasing attention is gene therapy. Gene therapy entails substituting flawed genes with normal ones by utilizing vectors derived from the outer shells of viruses, retaining the inherent properties of being able to target and enter specific cells. The modified gene is placed within this shell. Gene therapy can target germline or somatic cells - the latter being the most commonly used. The process for gene therapy is in-vivo or ex-vivo, depending on whether the transduction of the cells happens within or outside the body. Clinical trials in gene therapy have progressed tremendously, and even a few have reached approval by the FDA - but none yet for SCD or hemophilia. For both these diseases, the current treatments provide symptomatic relief but not long-lasting benefits. Currently, there are several gene therapy clinical trials ongoing for both conditions. This paper focuses on published results of sickle cell diseases and hemophilia and examines whether they are pointing towards short-term benefits or whether the effect is long-term.

Introduction

Gene therapy is an innovative approach to treating diseases. It involves the replacement of disease-causing genes with normal genes. For rare diseases, gene therapy is one step closer to truly personalized medicine. For example, hemophilia and sickle cell disease are two rare hematological disorders that have been targets of gene therapy explorations. One of the critical questions is whether gene therapy provides a long-lasting effect or a temporary correction of the disease manifestation.

Background

Sickle Cell Disease

Sickle cell disease (SCD), also known as sickle cell anemia, is an inherited blood disorder, mainly affecting people of African, Middle Eastern, or Indian descent, wherein a defect in the genes that produce the protein hemoglobin in red blood cells, causes them to appear curved instead of round discs. These ‘sickle-shaped” red blood cells have a more challenging time going through circulation, and when they become stuck, they break down quickly. The blockage of minuscule blood vessels causes frequent manifestations of painful episodes. In addition, the accelerated breakage of red blood cells causes anemia - a reduced number of circulating red cells - thus giving the disorder its name. People with SCD can have other complications in the long term, for example, degeneration of joints, strokes, a particular form of pneumonia (called acute chest syndrome), and kidney issues - ultimately resulting in a reduced life span. Currently, there are very few treatment options for SCD - all of which only treat the symptoms but not the root cause of the disease.

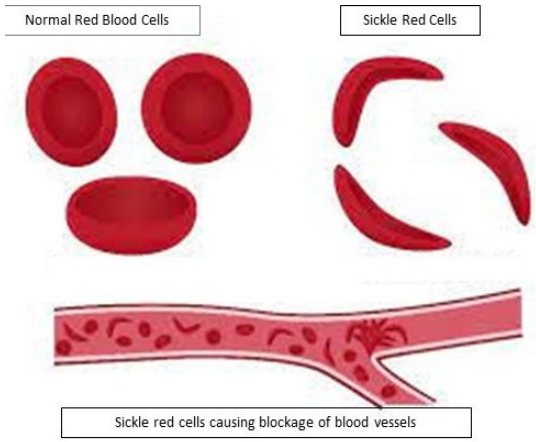
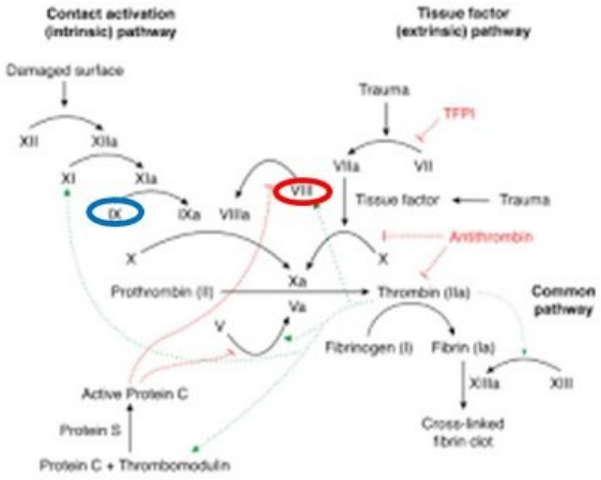


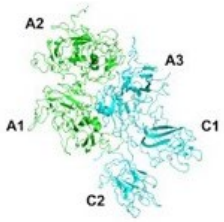
Figure 1. Normal blood cell vs. sickle cell blood cell.

Hemophilia

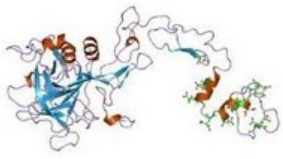
Similar to sickle cell disease, hemophilia also is an inherited disease. It predominantly affects males. Hemophilia is a disorder in which the body fails to clot due to the lack of specific proteins (also known as factors). There are two different types of hemophilia: hemophilia A and hemophilia B. The most common type is hemophilia A. This type results due to the lack of Factor VIII.

On the other hand, people with hemophilia B lack Factor IX. Both versions can be harmful to a person due to the uncontrolled bleeding that can occur. The severity of the disease is inversely proportional to the amount of factor protein in the blood. Treatment with replacing the missing protein through regular injections of factors has helped people with hemophilia. However, to be truly effective, the treatments must be taken regularly, from every couple of days to every few weeks, thus adding treatment burden to the lives of the people affected by hemophilia.





Factor VIII molecule



Factor IX molecule

Figure 2. The coagulation cascade shows where factors VIII and IX play a role in stopping bleeding.

Gene therapy

Gene therapy is the replacement of disease causing genes with normal genes. It has the potential to prevent or even be a cure for several diseases. There are two types of gene therapy: germline gene therapy and somatic cell gene therapy. Germline gene therapy delivers new genes to germ cells that pass on from one generation to the next. It may have long-lasting effects and can be a permanent cure for many people with a particular disease. While the disease is likely to be eliminated with this approach, germline gene therapy raises much controversy due to ethical reasons. As a result, it is often not used.

In contrast, somatic cell gene therapy is the transfer of new genes to somatic cells that are not inherited. In this approach, they only target the flawed cells. However, somatic cell gene therapy is likely not a permanent cure as the replaced cells eventually die. There are two approaches to somatic gene therapy: ex-vivo gene therapy and in-vivo gene therapy.

The names of these processes derive from where the corrective gene targets the defective cells. One is ex-vivo - where flawed cells are extracted from the body, manipulated to remove the defective gene, and replaced with the normal gene through a vector in a laboratory. The cells with the corrected gene return to the body. The second approach is in-vivo, where vectors containing the corrective gene are produced in a laboratory and injected into the patient. The vectors are designed to recognize and enter target cells inside the patient and deliver the corrected gene into the cells. Once the corrective genes are introduced into the body, they start producing the missing protein, thus fixing the symptoms of the disease.

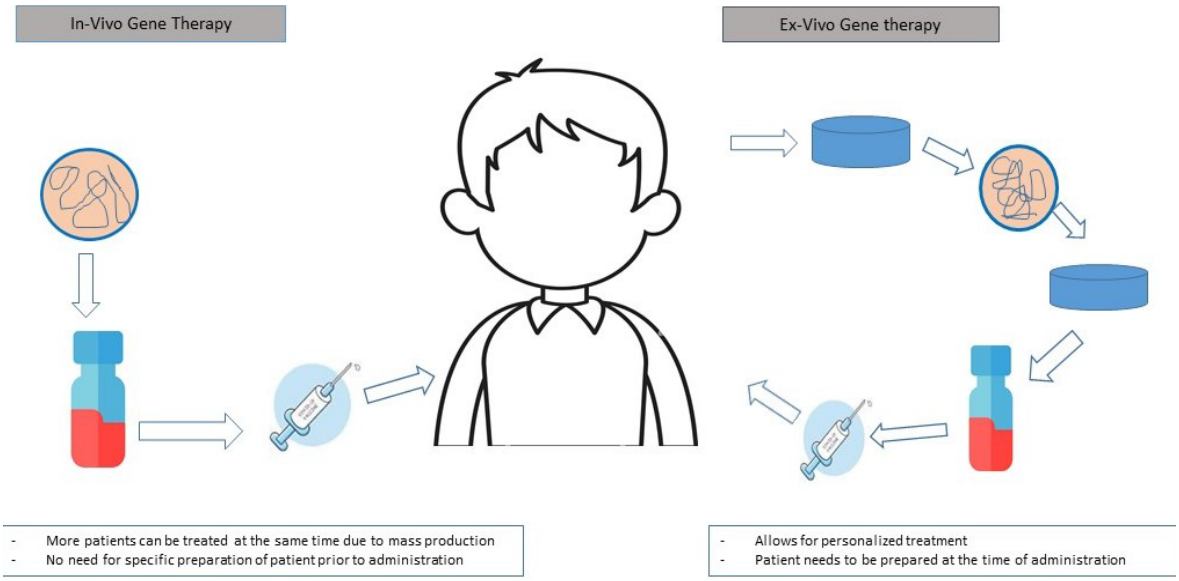


Figure 3. Diagram of how in-vivo and ex-vivo work.

In either of the approaches, gene therapy uses carriers called vectors to transfer DNA material to the targeted cells. There are two main classes of vectors: viral vectors and non-viral vectors. Viral vectors are derived from viruses designed to retain the critical properties that help deliver the DNA to the target cell. They use the outer shell of viruses, called the capsid, to enter the cell. The new genetic material inside the capsid is called the transgene. The capsid dissolves after the vector enters the cell, and the transgene either attaches to the DNA of the host cell or stays as a parallel structure called an episome. The new genetic material produces the protein that is missing. In non-viral approaches, the defective part of the DNA is covered by the unique DNA sequence, thus

allowing the RNA to read the corrected frame and thus produce the suitable protein. One example of this that is well known is CRISPR technology.

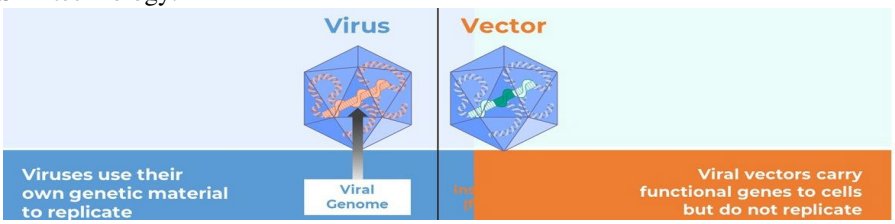


Figure 4. The differences between viruses and viral vectors. Adapted from US Food and Drug Administration. What is Gene Therapy?, Kay MA, et al. *Nat Med* 2001; 7(1):33–40, Thomas CE, et al. *Nat Rev Genet* 2003; 4(5):346–358.

Current Gene Therapy Programs for SCD and Hemophilia

SCD Gene Therapy

SCD gene therapy has become an active area of research, prompted by the limited treatment options for SCD. Since treatment of SCD has to target the bone marrow where red cells are produced, ex-vivo is the most commonly used technique. The bone marrow is stimulated to produce stem cells (precursors of red cells). These cells are collected and reformed with new genes to make normal hemoglobin. Giving high-dose chemotherapy to the patient creates space in the bone marrow to accommodate these new cells. Viral vectors or techniques like CRISPR introduce the gene to produce normal hemoglobin into the stem cells. The reformed cells are then transfused to the patient, returning to the bone marrow and producing normal hemoglobin.

Hemophilia Gene Therapy

Hemophilia gene therapy is another area of active research in hemophilia A and B. Here, the vector introduces the transgene to produce either Factor VIII or Factor IX into the liver through a vector. The liver is the site of protein production - therefore, it is the target organ for correcting hemophilia.

Clinical Trial Phases

All potential treatments are systematically studied in clinical trials to understand how well they work (efficacy) and how safe they are for patients (safety). This is true for gene therapy products as well. In Phase 1, the drug is studied in a small number of people (usually healthy volunteers) to understand its safety. In Phase 2, the drug is examined in patients with the disease for efficacy and continued safety. Phase 3 is the final step before the drug can be approved through a rigorous process by authorities like the Food and Drug Administration (FDA) for wide patient availability.

In this paper, we explore the current results of the clinical studies of gene therapy for SCD and hemophilia with the question of whether they offer temporary correction of symptoms or a more permanent solution.

Methods

In this analysis, we reviewed the literature for published results of gene therapy trials for SCD and Hemophilia. We looked for initial results to see if the gene therapy had worked and if the trials progressed from one phase to the next. We also looked for how long there was the persistence of the treatment effect.

Results

SCD Gene Therapy Trials

The table below summarizes the ongoing SCD gene therapy clinical trials:

TRIAL NUMBER	SPONSOR COMPANY	SUBJECTS PLANNED	SUBJECTS ENROLLED
NCT02151526 (Ages 5-37yrs)	BlueBird Bio	7	3
NCT02140554 (Adults)	BlueBird Bio	29	9
NCT02247843 (Adults)	UCLA	6	1
NCT02186418 (Ages 18-35 yrs)	Cincinnati Children's Hosp	10	Not reported
NCT03282656 (Ages 3-40 yrs)	Boston Children's Hosp	7	1

Figure 5. Table of active sickle cell trials. Adapted from Cavazzana, Marina & Mavilio, Fulvio. (2018). Gene Therapy for Hemoglobinopathies. Human Gene Therapy. 29. 10.1089/hum.2018.122.

The trials above show how much research has been done on SCD gene therapy. However, minimal treatments have progressed to the subsequent phase. The table above portrays that the trials have not made it out of phase one. This concludes that there is insufficient information to prove gene therapy is a long-lasting solution.

Hemophilia Gene Therapy Trials

Hemophilia A

There is one clinical trial of valroctogene roxaparvovec that has completed a Phase 3 trial. The results are below.

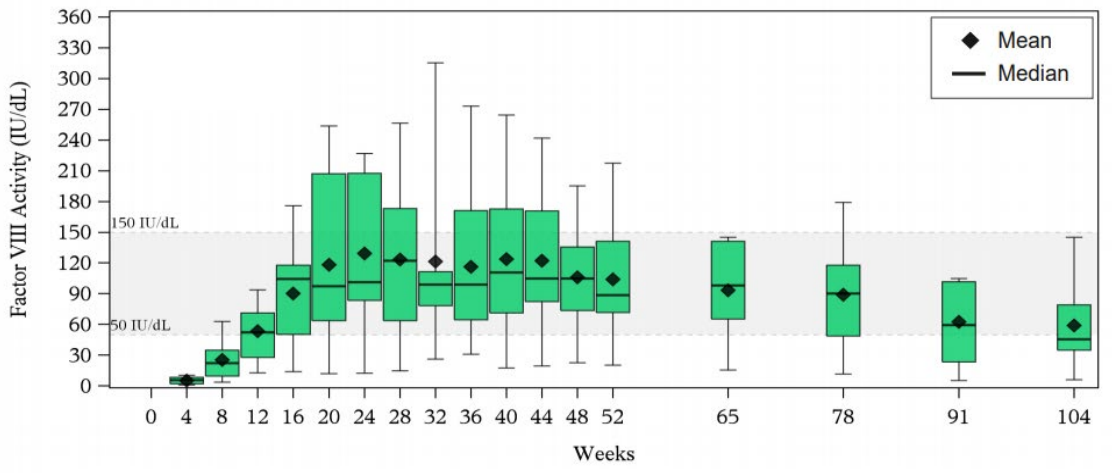


Figure 6. Data of Factor VIII was produced after gene therapy from BioMarin. Source from BioMarin Website

BioMarin developed a gene therapy called valoctocogene roxaparvovec for patients with hemophilia A. Each patient receives 6×10^{13}vg/kg of valoctocogene roxaparvovec. Figure six portrays the FVIII levels observed in this study. At first, the levels of FVIII started to increase. However, over time it gradually decreased, and the cells were not producing FVIII anymore.

Hemophilia B

There are several trials ongoing for hemophilia B. For example, researchers at Pfizer conducted a trial. They successfully demonstrated FIX production. In addition, they published data on the same patients five years after receiving gene therapy, shown below. This product is currently in Phase 3.

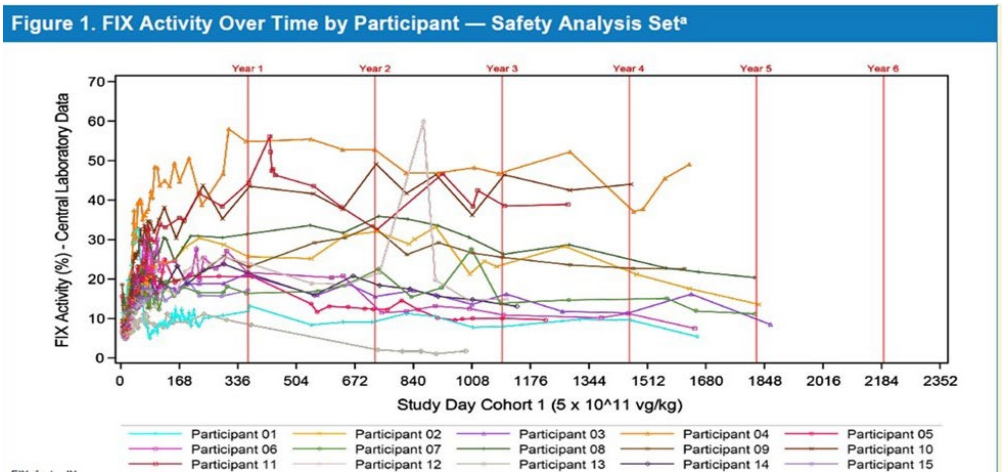


Figure 7. Factor IX measurements after a gene therapy program at Phizer. Source from Samelson-Jones et al., 2021.

Phizer conducted a study on fifteen participants with severe cases of Hemophilia B. Each patient received a gene therapy called findanacogene elaparvovec. They got a dose of $5X10^{11}$ vg/kg. The study was recorded for five years. The patients did not return to needing factor-infusion treatments and did not report any bleeding complications (Samelson-Jones et al., 2021). Figure seven represents Factor IX (FIX) measurements following the gene therapy program at Pfizer. The levels of FIX have been holding steady for over five years.

Discussion

Gene therapy aims to provide long-term relief from the symptoms of the disease by producing the corrected or missing protein. The desire is that this is a one-time treatment that provides lifelong protein production. However, the reality of long-term durability is not always the case. As we see in the table for sickle cell disease, gene therapy trials have not progressed out of phase 1. Furthermore, there is not enough information about SCD in gene therapy to determine if it is a long-lasting solution. To add, the challenges of establishing the transgene in the stem cells, and ensuring that the person's immune system does not eradicate the vector, have been a challenge for sickle cell researchers. Additionally, "one limitation of the gene therapy is that patients must first be treated with high-dose chemotherapy to eliminate old stem cells and make room for the modified stem cells, a process known as conditioning. Chemotherapy can be toxic and is associated with a small risk of cancer" (Columbia University, 2021). Furthermore, chemotherapy can be harmful to the patient. It can lower their immunity, make them very weak, and can potentially result in death or other serious issues.

On the contrary, hemophilia presented more successful results. The graph showed that the cells were developing the factor needed. In hemophilia, A showed an initial steady production of factor FVIII. Then, the levels of FVIII gradually declined. However, once the new gene was introduced to the cells in hemophilia B, they started to make the factor IX. Unlike hemophilia A, in hemophilia B, the cells continued to produce the factor IX several years after receiving gene therapy.

Conclusion

In conclusion, while gene therapy is an exciting innovation in treatment options, it has not offered a long-lasting solution to SCD or hemophilia. One reason could be that gene therapy targets somatic gene therapy. Somatic gene therapy does not allow the effects to be permanent since the modified gene is not passed on when the cell divides. SCD, in particular, does not seem to have made significant progress in having a long-lasting treatment with gene therapy. Additionally, the need for pre-treatment with toxic chemotherapy adds dangerous side effects to the current gene therapy process for SCD. In contrast, Hemophilia A gene therapy has progressed to Phase 3. The Phase 3 clinical trial results showed that initial high levels of FVIII were produced. However, the FVIII levels did not hold the same range they started and gradually lowered over time.

Hemophilia B, on the other hand, shows a more steady production of FIX up to five years after one single dose. The data presented encourages gene therapy to be a more permanent option for hemophilia B. Even though gene therapy could potentially be a cure for hemophilia B, other diseases still require life-long treatment. Some have no treatment options. Thus, many people continue to suffer. That is why it is essential to continue research in gene therapy to refine the techniques to create solutions where this could be a cure and not merely be a temporary fix to these devastating diseases.

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