SDM
WFH SHARED DECISION MAKING TOOL

GENE THERAPY FOR HEMOPHILIA A

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What is Gene Therapy?

Your genetic information is composed of multiple parts. Genes are the part of your DNA that provide instructions for your cells to make specific proteins, like factor proteins. Gene therapy is a treatment that provides your cells with a working copy of a gene. For hemophilia, gene therapy provides your cells with a working copy of the factor VIII (8) gene for hemophilia A or the factor IX (9) gene for hemophilia B, which allows your body to produce functioning clotting factors on its own, leading to long-term factor expression.

The corrected gene is delivered to the cells in something called a "vector." A vector is like a package that carries the functional gene to the cells that need it. A vector is a structure that originally came from a virus but has been modified to remove the parts that could cause illness. Once the vector is inside the body, it targets the specific cells that need the working gene: in hemophilia, these are your liver cells. The functional gene is then processed by your cells to produce working clotting factor proteins. Gene therapy does not change your own DNA but adds a healthy copy of the factor gene to your cells. Current therapies use adeno-associated viral (AAV) vectors, but there are multiple vector types, and there may be other delivery vectors in the future.

Gene Therapy

After the vector has done its job and delivered the working gene, the added gene remains within the liver cells, and the vector leaves the body naturally through urine, feces, blood, saliva, and semen. This is called vector shedding.

The goal of gene therapy is to enable a patient's body to make its own clotting factor to prevent bleeds, avoid regular prophylactic infusions, prevent further damage, and improve quality of life. Gene therapy can provide sustained and near-normal factor levels for years and eliminates the need for routine prophylaxis in the majority of patients who receive treatment.

What gene therapy treatments are available?

As of January 2024, three gene therapy products have been approved for the treatment of hemophilia (one for hemophilia A and two for hemophilia B). There are several other gene therapies in clinical trials for the treatment of hemophilia A and hemophilia B.

Each type of gene therapy has unique features that can affect how well it works in your body and whether it's the right choice for you. Your healthcare team can help you understand the different treatment options and how gene therapy might impact your life. Your healthcare team will consider your medical history, the severity of your hemophilia, and your personal preferences and goals to help you make an informed decision about gene therapy.

How is the mechanism of action for gene therapy different from other treatments for hemophilia?

The main treatment types for hemophilia are clotting factor replacement therapy, bispecific antibodies, re-balancing agents, and gene therapy. All these treatments help the blood clot more efficiently, but they all work in different ways.

Clotting factor replacement therapies temporarily increase factor levels by injecting the needed clotting factor protein directly into the blood of a person with hemophilia.

Bispecific antibodies are Y-shaped proteins that act as a bridge between factor IXa and factor X, which helps the blood to clot more efficiently. This antibody bridge mimics the function of the missing activated factor VIII (i.e., factor VIIIa-mimetic).

Rebalancing therapies restore the disrupted balance between the levels of anticoagulation (i.e., anti-clotting) factors and clotting factors in the blood, thereby improving blood clotting.

Gene therapy introduces a working copy of the missing clotting factor gene. Once the gene is introduced, the body can produce the missing protein and maintain adequate clotting factor levels, on its own, for an extended time.

How will I know if gene therapy is the right treatment choice for me?

Deciding to pursue treatment with gene therapy is an important decision that should be made after discussing your options with your healthcare team and loved ones. The decision should be based on the available evidence, your health history, your life goals, and your treatment preferences. Make sure you understand the possible benefits and risks associated with gene therapy. Take your time to think, reflect, and discuss your options with your healthcare team and others you trust.

Gene therapy is not for everyone. Some people will not be eligible, and some will not have access. If you are eligible and it is available to you, it is not guaranteed that you will respond to gene therapy. If you do respond to gene therapy, it is not possible to predict your level of response. At this time, you cannot re-do gene therapy, but if your therapy is not successful you can safely return to your prior treatment regimen or consider other treatment options. Keep in mind that gene therapy for hemophilia A and for hemophilia B are different, with different benefits and risks associated with treatment. For example, after gene therapy treatment, most patients with hemophilia A (~80%) and some with hemophilia B (20–50%) require treatment with additional medications (e.g., corticosteroids or other immunosuppressive medications) for several weeks to months for the treatment of immune reactions in the liver. There can be significant side effects associated with taking these medications, and your healthcare team is equipped to help you manage these side effects.

TREATMENT WITH GENE THERAPY

Who is eligible to receive gene therapy?

Treatment with gene therapy should be discussed in detail with your healthcare team. ROCTAVIAN (valoctocogene roxaparvovec) is approved for use in adults with hemophilia A.[1] Patients must not have pre-existing antibodies against the AAV5 vector and must not have a history of factor VIII (8) inhibitors.

New gene therapies may also be available through clinical trials. Generally, patients eligible for clinical trials are adults with severe or moderately severe hemophilia who are at least 18 years old; have been treated with factor replacement therapy or other types of treatment; have no evidence of advanced liver dysfunction and are otherwise healthy. If you meet these criteria, you may be able to participate in a clinical trial if your Hemophilia Treatment Center is involved in an ongoing clinical trial. Participation should be discussed with your healthcare team.

How is gene therapy administered?

Gene therapy is administered at a hemophilia treatment center by a single infusion into a vein in your arm. The infusion typically takes 1–4 hours, but you should plan for a full day at the treatment center. After the infusion, you will be monitored for several hours to make sure you are okay before going home.

What is the treatment frequency for gene therapy?

Gene therapy is a one-time-treatment and you will not require repeat infusions. If you do not respond to gene therapy, you are not currently eligible to receive gene therapy again, but you can return to other prophylactic therapies for treatment of your hemophilia.

EFFICACY OF GENE THERAPY

How will clotting factor levels be affected?

The effects of gene therapy will begin to appear approximately 3–4 weeks after treatment. If the treatment is successful, clotting factor levels will begin to increase approximately 3–4 weeks after treatment, and clotting factor levels will stabilize within a few months. After a few months, clotting factor levels will stabilize. Everyone responds differently to gene therapy, and it is not possible to predict what factor level someone will achieve or how long they will maintain that factor level.

After treatment with ROCTAVIAN for hemophilia A, average factor levels were 42% after 1 year, 23% after 2 years, and 15% after 3 years[1]. Studies are in progress to determine whether the factor levels will continue to decline. Longer-term data are available and could be discussed with your healthcare team.

Factor VIII levels in People with Hemophilia A Up to Three Years After Treatment

Level of FVIII expression[1]	Percentage of people with hemophilia A after ROCTAVIAN treatment		
	Year 1 (N = 134)	Year 2 (N = 134)	Year 3 (N = 19)
0–3%	10%	15%	26%
3–5%	2%	10%	11%
5–15%	17%	34%	42%
15–40%	34%	26%	5%
>40%	31%	13%	16%

Note: there are cases where people achieve supranormal factor levels >150%; these cases will require frequent monitoring

How will gene therapy affect my annual bleeding rate?	In phase 3 clinical trials for ROCTAVIAN, people with hemophilia A had very few bleeding events and averaged 2.6 bleeds per year, with 0.8 bleeds per year requiring treatment.[1] Most people (74%) had zero bleeds requiring treatment.[1]
How will gene therapy affect my use of prophylaxis?	Patients will continue prophylactic treatment until they produce their own factor, which typically takes a few weeks. Not all patients will produce enough factor to stop prophylactic treatment. In clinical trials, 96% of patients who received ROCTAVIAN did not need to restart prophylaxis 2 years after treatment.[1]
How long can I expect the effects of gene therapy to last?	We do not know how long the effects of gene therapy will last. As of June 2023, patients have been followed for three years for hemophilia A and two years for hemophilia B in clinical trials. There are differences in how long gene therapy lasts between hemophilia A and hemophilia B, please discuss the latest data with your healthcare team.

SAFETY OF GENE THERAPY

Is gene therapy safe?	Clinical trials evaluate whether new treatments are safe and effective. In the case of gene therapy for hemophilia, clinical trials have been run to make sure that the treatment is safe for people to use. ROCTAVIAN is approved for use in the United States and Europe for the treatment of Hemophilia A. Gene therapy has known warnings and precautions that should be discussed with your healthcare team prior to deciding on a treatment plan.
What are the possible side effects (adverse reactions) of gene therapy?	The most common side effects (adverse reactions) following treatment with ROCTAVIAN were nausea, fatigue, headache, infusion related reactions, vomiting, and abdominal pain.[1] The most common laboratory abnormalities included increases in ALT, AST, and factor VIII activity. Infusion-related reactions included hypersensitivity reactions, anaphylaxis, nausea, fatigue, and headache. Patients are closely monitored during the infusion and these symptoms, which may temporarily interrupt treatment, can be treated, and usually resolve quickly.
Are there any known serious side effects of gene therapy?	Some important side effects are known and can be controlled. Most people with hemophilia A (80%)[1,2] will experience abnormal increases in liver enzyme levels following gene therapy. These liver changes can be controlled with additional medications (e.g., corticosteroids or other immunosuppressive medications) for several weeks to months. There can be significant side effects associated with taking these medications, however they are generally manageable and reversible; your healthcare team is equipped to help you manage these side effects. Because of these liver changes, it is recommended that patients abstain from alcohol for at least one year, and thereafter limit their alcohol use.
What are the long-term side effects of gene therapy?	Longer-term risks include potential impacts to liver health.[2] Clinical trials are ongoing, and current available data is limited to ~8 years; therefore the long-term risks are not fully known. No known cancers related to gene therapy have been observed to date.

MONITORING AND FOLLOW-UP AFTER GENE THERAPY TREATMENT

How often will you need follow up and monitoring after gene therapy?	Treatment with gene therapy requires regular follow-ups. The typical follow-up schedule in year one is 1–2 times per week for the first six months and every 1–4 weeks for the next 6 months. Most of these visits will be laboratory visits that may only require a blood draw. In year 2, visit frequency may decrease to once every three months. After year 2, visit frequency may decrease to once every six months. Visits may be more frequent for patients with factor levels less than 5%. These visits will help your healthcare team monitor your health and factor levels to make sure the treatment is still working effectively. Follow-up will be a mix of laboratory visits and office visits. You will need to continue to see your healthcare team for regular check-ups even after the initial follow-up period is over to ensure that you continue to receive the best possible care and support for your hemophilia.
Do I need to register in a patient registry after gene therapy?	The best way for researchers to monitor how well gene therapy works over the long-term is for all patients who receive gene therapy to be followed in a registry. The WFH Gene Therapy Registry (GTR) is designed so that every patient, no matter where they live, can participate.[3] Participation in the registry is voluntary but recommended. You can ask your healthcare team to sign you up for the WFH GTR.

LIFE AFTER GENE THERAPY TREATMENT

Can I stop gene therapy?	Once gene therapy has been administered, the added gene cannot be stopped or removed. It is important to carefully consider the potential benefits and risks of gene therapy before deciding to undergo the treatment.
Will I still have hemophilia after gene therapy?	Gene therapy is not a cure for hemophilia, but successful treatment can eliminate the burden of prophylaxis, reduce bleeding, and improve quality of life. Studies have shown that gene therapy increases factor levels in most, but not all, patients, sometimes even to normal levels. This can help reduce or eliminate bleeding and the need for regular factor infusions. While normal levels may be achieved by some, for others, the severity of hemophilia may be improved.
If gene therapy is not successful, can I return to my prior treatment regimen?	If gene therapy for hemophilia is not successful, you will be able to safely return to your prior treatment regimen or another standard of care treatment.
Will I still need to use other treatments for hemophilia?	It is possible that you may not need to use regular prophylaxis or factor replacement therapy once your factor levels reach a level where most bleeds would stop. The majority of people in clinical trials did not need to resume prophylaxis or take treatment for bleeding events in clinical trials. It is recommended that you continue to work closely with your healthcare team and follow their recommendations for managing your hemophilia. In some cases, such as bleeding, trauma, and surgeries, additional treatment may still be necessary.

Will gene therapy heal my existing joint damage?	Gene therapy is unlikely to reverse existing structural joint damage, but may reduce other joint symptoms.
How will my quality of life be affected by gene therapy?	Gene therapy for hemophilia has the potential to improve a patient's quality of life. Many, but not all, patients who have undergone gene therapy report increased freedom and improved ability to engage in physical activities without fear of bleeding.[4] With successful gene therapy, patients may no longer require regular prophylaxis and may experience a significant reduction in bleeding episodes.
What will happen in the event of a bleed or injury or if I need surgery?	The need for treatment following a bleed, injury, or because of surgery will depend on how much factor your body is producing. Each person's response to gene therapy is different, and impossible to predict. There is also no guarantee that every bleed or injury will have the same treatment needs. This should be discussed with your healthcare team. In most cases, you are advised to treat a bleed with usual replacement therapy products and record all details.

GENE THERAPY AND FAMILY PLANNING

Can the effects of gene therapy be passed on to my future children?	Gene therapy for hemophilia A provides a functional copy of the factor VIII (8) gene to the liver. Gene therapy does not change the DNA in your reproductive cells and therefore, hemophilia can still be passed on to future children. This means that if a person with hemophilia receives gene therapy, their children will not inherit the working gene. Gene therapy only helps the person who receives it, not their future children.
Will gene therapy impact my ability to have children?	Men: No, gene therapy will not affect your ability to have children. However, the vector may be present in semen (as it is released from the body) for a varying period of time after receiving gene therapy. Although there is very little risk that it affects semen, it is recommended that men use contraceptive measures to prevent pregnancies until the vector is no longer present (i.e., 6 to 12 months).[1] Women: No data are available to recommend the duration of contraceptive measures in women of childbearing potential. While women are eligible for gene therapy, it is not recommended in women of childbearing potential. Gene therapy is also not recommended in women who are pregnant or breastfeeding.[1]

GENE THERAPY TREATMENT IN CHILDREN AND ADOLESCENTS

Is gene therapy approved for use in children and adolescents?	Gene therapy is only approved for use in adults. Studies are ongoing in pediatric patients.

OTHER RESOURCES

What is the World Federation of Hemophilia Gene Therapy Registry (WFH GTR)?	The WFH GTR is a prospective, observational, and longitudinal registry designed to collect long-term data on people with hemophilia who receive gene therapy globally.[3] Participation in the registry after receiving gene therapy is voluntary but recommended. This registry is the best way to capture long-term data on gene therapy and ensure the safety of gene therapy for patients.
Where can I find more information on gene therapy or gene therapy for hemophilia?	American Society of Gene and Cell Therapy A Guide for Patients and Caregivers. All About Hemophilia Gene Therapy. Canadian Hemophilia Society. EHC Gene Therapy A Practical Guide Book ISTH: Gene Therapy National Hemophilia Foundation. Frequently Asked Questions WFH Gene Therapy Registry The Hemophilia Gene Therapy Patient Journey: Questions and Answers for Shared Decision-Making. Wang M, Negrier C, Driessler F, Goodman C, Skinner MW.

1 Prescribing information and Phase 3 studies from approved gene therapy products. See the SDM Tool References Page.

2 Pierce GF, Iorio A. Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes. Haemophilia 2018;24 Suppl 6:60-67.

3 Konkle BA, Coffin D, Pierce GF, et al. World Federation of Hemophilia Gene Therapy Registry. Haemophilia 2020;26:563-564.

4 Miesbach W, Klamroth R. The Patient Experience of Gene Therapy for Hemophilia: Qualitative Interviews with Trial Patients. Patient Prefer Adherence 2020;14:767-770.

Last reviewed: March 2024
This is a living document that will be updated with new evidence twice per calendar year. The cutoff dates are June 30 and December 31, with updates taking place in the following month(s). Any new evidence after these cutoffs will be included in the next update.