Cell & Gene Therapy Overview

Traditional medications that treat chronic disease often require frequent ongoing administration for the entirety of a patient's life. They work to manage symptoms and disease progression, but do not provide a cure for most disease states. This shortcoming is especially evident for treating diseases that are caused by mutations in a single gene at birth or genetic mutations that happen later in life. It is estimated that more than 6,000 diseases are caused by genetic mutations and may affect more than 350 million people worldwide.

Cell and gene therapies (CGTs) are relatively new treatment options. Both offer a potentially curative treatment in a single dose by alleviating the underlying cause of the genetic or acquired disease. However, CGTs work differently. In the simplest terms, gene therapies work by replacing or modifying the disease-causing gene to treat or cure a disease. Cell therapy uses new cells to treat a particular health condition. Specifically, new cells can be transplanted to replace or repair damaged cells that cause disease, or they can function as an immune cell treatment that targets and removes dysfunctional cells.

To date, there are thirty-four FDA approved CGTs in the United States, with seven of those being approved during 2023. This is significant considering the first one wasn't approved until 2017. Currently, there are over 1,500 ongoing clinical trials for such therapies with the majority focusing on cancer treatment. Many known challenges exist in the development and approval process for CGTs and the pipeline remains robust and new trials are starting at an increasing rate.

Gene Therapy

Gene therapy is a medical approach that treats or prevents disease by correcting the underlying genetic problem. Most often, gene therapy works by adding new copies of a gene that is broken, or by replacing a defective or missing gene in a patient's cells with a healthy version of that gene. Both inherited genetic diseases like hemophilia and sickle-cell disease (SCD), as well as acquired disorders like leukemia have been treated with gene therapy.

To insert new genes directly into cells, scientists use a vehicle called a "vector." There are different types of vectors, but all are genetically engineered to deliver the necessary genes for treating the disease. Viruses are currently the most used vectors in gene therapies because they have a natural ability to deliver genetic material into cells. Before a virus can be used to carry therapeutic genes into human cells, it is modified to remove its ability to cause infectious disease.

Gene therapy can be used to modify cells inside or outside the body. When a gene therapy is used to modify cells inside the body (in vivo), the vector carrying the gene is injected directly into the patient. When gene therapy is used to modify cells outside the body (ex vivo), blood, bone marrow, or another tissue is taken and separated out into specific cell types in the lab. The vector containing the desired gene is introduced into these cells. The cells are later injected into the patient, where the new gene is used to produce the desired effect.

Roctavian™ (valoctocogene roxaparvovec) is an example of an in vivo gene modification therapy that was approved in June 2023. It is a single dose IV infusion for patients diagnosed with severe hemophilia A. Hemophilia A is a lifelong bleeding disorder caused by a single genetic defect that reduces the production of a protein called clotting factor VIII. Patients living with hemophilia A typically require regular

prophylactic treatment with clotting factor to prevent bleeding episodes. Roctavian uses a viral vector to deliver a functional gene to liver cells that enables the body to produce Factor VIII on its own. As a result, patients treated with Roctavian may need very little if any prophylactic Factor VIII therapy. In fact, in the most recent study with 134 male patients over 3 years, the need for prophylactic therapy decreased by 98%. At the end of year 3, 92% of patients remained off prophylaxis therapy.

Gene editing is a newer technique being used for gene therapy. Instead of adding new genetic material, gene-editing tools change the existing DNA in the cell allowing genetic material to be added, removed, or altered at precise locations of the gene. Casgevy™ (exagamglogene autotemcel) was the first FDA-approved therapy that uses the CRISPR gene-editing technology. It was approved in December 2023 for the treatment of SCD, an inherited blood disorder caused by a defective gene. The disease affects hemoglobin, the protein that helps red blood cells transport oxygen throughout the body. Red blood cells are usually round and flexible, so they move easily through blood vessels. In SCD, the hemoglobin gene is faulty causing some red blood cells to be shaped like sickles or crescent moons. These sickle cells also become rigid and sticky, which can slow or block blood flow. Restricted blood flow and lack of oxygen causes significant acute pain, infections, and damage to internal organs. With Casgevy's gene editing technology, the patient's blood cell precursors are isolated and genetically modified to make high levels of fetal hemoglobin, a form of hemoglobin produced during fetal development that is more effective at carrying oxygen than its adult counterpart. These modified cells are administered to the patent and expected to populate the blood with healthy hemoglobin-producing blood cells. The safety and effectiveness of Casgevy was evaluated in an ongoing single-arm trial. The primary efficacy outcome was freedom from severe acute pain episodes for at least 12 consecutive months during the 24-month follow-up period. A total of 29 (93.5%) of the 31 patients achieved this primary outcome.

Cell Therapy

Cell therapy treats or fights diseases directly by restoring or altering certain sets of cells or by using cells to carry a therapy through the body. With cell therapy, cells are cultivated or modified outside the body before being injected into the patient. The cells may originate from the patient (autologous cells) or a donor (allogeneic cells).

Omisirge® (omidubicel-onlv) is a cell therapy approved in April 2023 to lower the risk of infection in patients with blood cancers. It does this by helping the body recover more quickly from cancer treatments that kill normal blood cells along with blood cancer cells. Omisirge is a one-time, intravenous treatment made up of human donor stem cells from umbilical cord blood that is processed with a form of vitamin B3 to help stimulate the production of white blood cells. Each treatment is specifically manufactured for each patient and takes 30 days from the start of manufacturing. Clinical trial results demonstrated that blood cancer patients treated with Omisirge had a lower rate of infection following transplantation as well as a quicker recovery of healthy blood cells. Studies also indicate that Omisirge-treated patients have shorter durations of hospitalizations, shorter intensive care unit stays, fewer procedures and transfusions when compared to patients who did not receive the cell therapy. However, Omisirge did not significantly improve non-relapse mortality, disease relapse, disease-free survival, or overall survival in comparison to standard umbilical cord stem cell transplant.

Chimeric Antigen Receptor T cell (CAR-T) Therapy

CAR-T therapy is a cell-based gene treatment that combines the technologies of CGT. Cell therapy introduces cells to the body that have a particular function to help treat a disease. In CAR-T therapy, the

cells are genetically altered to give them a special function. Specifically, CAR-T cell therapy introduces a gene to a person's T cells, which are a type of immune cell. This gene provides instructions for making a protein, called the chimeric antigen receptor, that attaches to cancer cells. The modified T cells can specifically attack cancer cells.

Kymriah® (tisagenlecleucel) was the first FDA approved CAR-T therapy in 2017 for the treatment of leukemia. It is manufactured specifically for each patient by collecting their T cells, inserting a genetic code, and reintroducing those cells into the patient. The inserted code tells the T-cell how to fight leukemia. Treatments such as Kymriah are generally reserved for cancers that have not responded to traditional treatment. A clinical trial showed that 82% of children and young adults who were treated had their cancer go into remission. In fact, the first patient treated with Kymriah for pediatric leukemia celebrated 10 years in remission during 2023. The most recent analysis of this study reported that the 5-year relapse-free survival of patients who initially achieved a complete response after Kymriah administration was 49%.

Risks

While CGTs hold promise to treat many diseases, they are still relatively new approaches to treatment and may have associated risks. Potential risks for cell therapies include fatal infusion reactions and graft-versus-host disease. Gene therapy risks include certain types of cancer, severe immune response, allergic reactions, or damage to organs or tissues if an injection is involved.

In November 2023, the FDA made a formal announcement regarding safety risks associated with CAR-T therapies. Specifically, the FDA said it had received reports of T-cell malignancies, including chimeric antigen receptor CAR-positive lymphoma, in patients who received treatment with CAR-T cell immunotherapies. Reports were received from clinical trials and/or post-marketing adverse event data sources. The FDA has determined that the risk of T-cell malignancies is applicable to all currently approved genetically modified CAR-T cell therapies which include the following: Abecma® (idecabtagene vicleucel), Breyanzi® (lisocabtagene maraleucel), Carvykti® (ciltacabtagene autoleucel), Kymriah® (tisagenlecleucel), Tecartus™ (brexucabtagene autoleucel), and Yescarta® (axicabtagene ciloleucel). Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T cell malignancy and is evaluating the need for regulatory action. Patients and clinical trial participants receiving treatment with these products should be monitored for potential new malignancies their entire life.

Cost

Although CGTs are innovative and potentially life altering treatment options, they are also associated with very significant healthcare costs. The average cost of gene therapy is between $2 million and $3 million per dose. While cell therapy prices are more variable, they can cost up to $1 million depending on the indication and type of product.

Theoretically, the high price of these treatments is offset by the potential lifetime cost of other, more traditional therapies. However, with such a high upfront price, payers restrict coverage. For example, Hemgenix® (etranacogene dezaparvovec-drib) is currently the most expensive medication in the United States at approximately $3.5 million. Approved by the FDA in 2022, it is the first gene therapy for adults with hemophilia B, a genetic bleeding disorder caused by a mutation in the Factor IX gene. This mutation prevents the body from expressing proteins needed to clot blood or stop bleeding. Left untreated,

prolonged bleeding caused by this condition can significantly impact a patient's joints, organs, and nervous system. The standard treatment for hemophilia B is lifelong frequent infusions to replace clotting factor, maintain normal blood levels, and prevent excessive bleeding. The average total medical cost of Factor IX treatment can be over $700,000 annually. Therefore, lifetime costs can total up to $20 million per person. The Institute for Clinical and Economic Review (ICER) determined that a fair price for Hemgenix is approximately $2.9 million, well below the actual cost. Additionally, ICER noted that a gene therapy such as Hemgenix becomes more cost effective the more durable it is. As of December 2023, men participating in an ongoing multinational trial with severe or moderately severe hemophilia B continue to display low bleeding rates and 94% have remained free from continuous prophylactic therapies for at least three years following the single dose treatment. If CGTs like Hemgenix are able to maintain their positive clinical response with minimal adverse events for many years to come, then the large upfront treatment cost may be justified.

Pipeline

Cellular and gene therapy-related research and development in the United States continues to grow at a fast rate, with a number of products advancing in clinical development. Fidanacogene elaparvovec and Lifileucel are two therapies that could be approved by the FDA in the next 6 months.

Fidanacogene elaparvovec is an investigational one-time gene therapy for hemophilia B that contains a high-activity variant of human coagulation Factor IX (FIX) gene. The goal of gene therapy is to enable hemophilia B patients to produce FIX themselves via this one-time treatment rather than needing regular intravenous infusions of FIX, as is the current standard of care.

In June 2023, the FDA accepted the biologics license application based on positive results from a Phase 3 study. In this trial, fidanacogene was associated with a 71% reduction in annualized bleeding rate (ABR) for all bleeds from week 12 to month 15 after treatment. The gene therapy was also generally well tolerated. If approved, fidanacogene elaparvovec would be the second gene therapy treatment for hemophilia B and a direct competitor to Hemgenix. The FDA-approved prescribing information for Hemgenix shows that ABR for all bleeds was reduced by 54% during months 7-18 in a comparable study. The potential projected cost for fidanacogene is estimated to be approximately $2.5 million.

Lifileucel is a single dose experimental treatment for a type of advanced skin cancer called melanoma. It utilizes immune cells called tumor infiltrating lymphocytes and is designed for patients who have experienced disease progression after previous treatment. The therapy involves altering a patient’s own cells, which are extracted from a tumor and then re-engineered. Ultimately, rejuvenated cells are reinfused back into the body.

The regulatory application was supported by data from a phase 2 trial that enrolled 153 patients. The overall response rate was 31.4% with eight complete responses and 40 partial responses. Median overall survival was 13.9 months and progression-free survival was 4.1 months. Study data suggests that lifileucel also has a favorable safety profile. If approved, lifileucel would be the first one-time cell therapy available to treat a solid tumor cancer that does not respond to first line therapies.

Gene modification and cellular therapies hold promise to be life-changing medical treatments for a wide range of diseases such as cancer, hemophilia, SCD, muscular dystrophy, cystic fibrosis, and many others. These groundbreaking therapies are bringing hope to patients with previously incurable rare conditions. While CGTs are extremely expensive, they are potentially curative and prevent or alleviate the need for

long-term adherence to often complex maintenance medications. The resulting possibility of health care savings and the impact on quality of life is significant but still needs to be proven. Only time will tell if the clinical effectiveness and safety profiles of CGTs will remain favorable long term to better justify their cost and the hope they currently provide.

References

1. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products
2. https://med.stanford.edu/cdcm/CGT.html?tab=proxy
3. https://www.genome.gov/
4. https://www.mayoclinic.org/tests-procedures/gene-therapy/about/pac-20384619?p=1
5. https://www.fda.gov/consumers/consumer-updates/how-gene-therapy-can-cure-or-treat-diseases
6. https://www.nhlbi.nih.gov/health/genetic-therapies
7. https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/cell-and-gene-therapy-overview-current-landscape-and-future-trends/
8. https://asgct.org/education/more-resources/gene-and-cell-therapy-faqs#:~:text=Gene%20therapy%20involves%20the%20transfer,gene%20therapy%20and%20cell%20therapy.
9. https://medlineplus.gov/genetics/understanding/therapy/mrnavaccines/
10. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-investigating-serious-risk-t-cell-malignancy-following-bcma-directed-or-cd19-directed-autologous
11. https://www.genengnews.com/insights/cell-and-gene-therapy-manufacturing-costs-limiting-access/
12. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7986360/
13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10294746/