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 to traditional medications. 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, the EMA has approved over 19 CGTs in Europe, including six CAR-T therapies. Currently, there are over 1,500 clinical trials ongoing for such therapies, the majority focusing on cancer treatment. Many known challenges exist in the development and approval process for CGTs, but 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 haemophilia and sickle-cell disease (SCD), as well as acquired disorders like leukaemia 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 August 2022 by the EMA. It is a single dose intravenous (IV) infusion for patients with severe haemophilia A. Haemophilia 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 haemophilia 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 enable the body to produce factor VIII on its own and prevent or reduce the recurrence of bleeding. As a result, many patients treated with Roctavian may no longer need prophylactic factor VIII therapy, as shown in a study of 134 male patients who received Roctavian and were then monitored following treatment. At the end of year 3, 124 of the patients (92%) 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 approved therapy that uses the CRISPR gene-editing technology. It was approved in November 2023 by the UK's Medicines and Health Products Regulatory Agency (MHRA), and in December 2023 it received positive opinion from EMA for the treatment of SCD, an inherited blood disorder caused by a defective gene. The disease affects haemoglobin, 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 haemoglobin 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 foetal haemoglobin, a form of haemoglobin produced during foetal 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 haemoglobin-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).

Ebvallo® (tabelecleucel) was the first allogenic cell therapy to be approved by EMA. It is used for patients over two years with a very rare type of cancer, relapsed or refractory Epstein-Barr virus positive posttransplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. Ebvallo® is made in a laboratory from T-cells (a type of white blood cell) from a healthy human donor who is immune to the Epstein-Barr virus. Each treatment is specifically manufactured for each patient, with the cells being individually selected to match with the patient receiving Ebvallo. Ebvallo is given as an IV injection and treatment continues over several weeks.

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 EMA approved CAR-T therapy in 2018 initially for the treatment of two blood cancers; acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL). 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 leukaemia. 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. 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%. The first patient treated with Kymriah for paediatric leukaemia celebrated ten years in remission in 2023.

Risks

While CGTs hold promise to treat many diseases, they are still a relatively new approach 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 January 2024, the EMA safety committee initiated a signal procedure to review data on secondary cancers related to T-cells, including T-cell lymphoma and leukaemia for the six CAR-T medicines approved in the EU. The committee is reviewing evidence from the EU's adverse reactions database, following which they will decide on the need for any regulatory action. The EMA acknowledged that secondary cancers were considered a potential risk at the time of authorisation of all six CAR-T medicines and included in the risk management plans for these products. Additionally, the EMA stated that close monitoring is already in place, with a requirement that the marketing authorisation holders of these products must regularly submit interim results from ongoing long-term safety and efficacy studies.

A similar review was also announced by the FDA in November 2023.

Cost

Although CGTs are innovative and potentially life altering treatment options, they are also associated with very significant healthcare costs, sometimes close to €2 million per treatment

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, some payers may restrict coverage. Safety, efficacy, epidemiology, and clinical data are key to informing coverage decisions. Increasingly, performance-based reimbursement agreements are being negotiated between payers and manufacturers for CGTs. They enable manufacturers to demonstrate that their products can reduce overall health expenditure by providing long term clinical benefits and meaningful impacts to patients.

Pipeline

CGT-related research and development in Europe continues to grow at a fast rate, with several products advancing in clinical development.

CGTs hold promise to be life-changing medical treatments for a wide range of diseases such as cancer, haemophilia, SCD, muscular dystrophy, cystic fibrosis, and many others. These groundbreaking therapies are bringing hope to patients with previously incurable rare conditions. While the upfront costs of CGTs are high, 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 favourable in the long term to better justify their cost and the hope they currently provide.

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