CTLA4 Haploinsufficiency

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Gene Therapy in Action is a digital publication casting an important spotlight on rare diseases and cancers. This series highlights the increasingly critical role of genetic engineering (also called "gene therapy" or "gene transfer") in the clinical landscape with respect to developing novel and effective therapeutics for the treatment of life-threatening conditions with an urgent unmet medical need. This blog is for educational purposes only and is not intended to replace the advice of your doctor or other health care provider.

What is CTLA4 Haploinsufficiency?

CTLA4 haploinsufficiency (sometimes referred to as CHAI disease) is a rare genetic disorder of the immune system that results in immune deficiency and dysregulation and can lead to development of autoimmune disorders. CTLA4 haploinsufficiency is characterized by excessive immune cells (lymphocytes) that infiltrate non-lymphoid organs including the intestines, lungs, central nervous system, bone marrow, and kidneys. Intestinal disease (enteropathy) and diarrhea are common. Enlargement of the lymph nodes (lymphadenopathy) and spleen (hepatosplenomegaly) and respiratory infections are also common. People with CTLA4 haploinsufficiency may also experience a number of autoimmune disorders, including thrombocytopenia (low blood platelet count) and neutropenia (low neutrophil count), hemolytic anemia, thyroid disease, diabetes, arthritis, psoriasis, vitiligo, or alopecia. Due to the immune dysfunction caused by the disease, there may also be an increased risk of developing cancers such as lymphoma.

Some people are more severely affected by CTLA4 haploinsufficiency than others, possibly due to lifestyle, infection history, or other genetic factors. According to the Genetic and Rare Diseases Information Center (GARD), fewer than 1,000 people have this disease in the United States. Symptoms of CTLA4 haploinsufficiency typically arise in early childhood into adulthood, often beginning with recurrent sinus and lung infections. Diagnosis is based on clinical symptoms, laboratory findings, and genetic testing.

What Causes CTLA4 Haploinsufficiency?

Identified in 2014, CTLA4 haploinsufficiency is a primary immune deficiency disease (PIDD) caused by mutations in the cytotoxic T lymphocyte antigen 4 gene, CTLA4. Normally, the gene results in the production of the CTLA4 protein, which is found on the surface of T-cells and functions to regulate immune cells, slowing down and controlling the action of the immune system. A mutation in just one copy of the gene (individuals inherit two copies of CTLA4, one from each parent) is sufficient to cause the disease, leading to abnormal T cell activity, lower levels of antibody-producing B cells, higher levels of autoimmune B cells, and infiltration of immune cells into organs. Because one mutated CTLA4 copy can lead to disease development, CTLA4 haploinsufficiency (having a single working copy of CTLA4) is considered an autosomal dominant-inherited disease. If a parent has a CTLA4 mutation, they have a 50% chance of passing the mutation to their children, though not all family members with the mutation will necessarily develop disease symptoms.

Treatments for CTLA4 Haploinsufficiency

Treatment for CTLA4 haploinsufficiency is typically based on the person's clinical condition and may include standard therapies for autoimmune conditions and immunoglobulin deficiencies. This may include immunoglobulin (Ig) replacement therapy, treatment with antibiotics to prevent infection, or immunosuppressive therapy.

Currently, one medication approved by the United States Food and Drug Administration (FDA) for people with rheumatoid arthritis and certain types of psoriasis, called abatacept, has shown to also be effective in patients with CTLA4 haploinsufficiency. The drug mimics the action of the CTLA4 protein and reduces immune activity. Clinical trials studying abatacept specifically as a treatment for people with CTLA4 haploinsufficiency are ongoing. Other immunosuppressants, including prednisone (systemic steroid), sirolimus (inhibits activation of T and B cells), and rituximab (antibody directed at B-cells) may also be considered. Hematopoietic stem cell transplantation (HSCT) is another option for treating primary immunodeficiency diseases such as CTLA4 haploinsufficiency. Once CTLA4 haploinsufficiency is diagnosed and managed appropriately via treatment of associated inflammation, autoimmunity, or infection, individuals with this disease live relatively normal lives. Several medical specialists may be required to maintain the individual's quality of life.

Gene Therapy Highlights for CTLA4 Haploinsufficiency

While treatment options for CTLA4 haploinsufficiency are available, efficacy and safety of these treatments vary, and many require multiple doses for the life of the patient, consuming their time and resources. Given the association between mutations in the CTLA4 gene and the development of CTLA4 haploinsufficiency, gene therapy presents an attractive approach for development of therapeutic strategies for treating the disease.

In general, gene therapy, or gene transfer, is the process of introducing genetic material into the body for one of several purposes: to introduce a functional copy of a dysfunctional gene, to silence ("turn-off") the expression of a harmful or toxic gene, to introduce gene editing components to correct the disease-causing mutation, or to introduce new or modified genes into the body to help treat a disease.

At the time of this publication, there are no open clinical trials investigating a gene therapy specifically for the potential treatment of CTLA4 haploinsufficiency. Nevertheless, gene therapy treatments for inborn errors of immunity that cause primary immune regulatory disorders like CTLA4 haploinsufficiency are being developed. Below we highlight some of the therapeutic techniques that could lead to new treatment options for CTLA4 haploinsufficiency in the future.

CTLA4 Haploinsufficiency

Highlight #1: CRISPR/CAS9 editing

Pre-clinical studies are underway for the treatment of CTLA4 haploinsufficiency using therapeutic gene editing to correct the CTLA4 gene mutations. Cells are retrieved from a patient via leukapheresis (blood is drawn from the patient and the white blood cells are separated from the sample) and are then modified ex vivo (outside of the body) by inserting a clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) system. The CRISPR/Cas9 system recognizes a specific sequence in the DNA of the gene of interest, in this case CTLA4, and makes a cut in the DNA at the appropriate location. Template DNA with the correct CTLA4 sequence is then used along with the person's own cell machinery to repair the mutated gene sequence on the CTLA4 gene. The CRISPR/Cas9 system and template DNA are inserted into the cells through electroporation (high voltage applied to cells to allow entrance through the cell membrane) or with help of a viral vector (modified virus that delivers genetic material into cells). After gene editing, the cells are then returned to the patient and infused, providing the patient with their own cells now producing functional CTLA4. Proof-of-concept studies have demonstrated that CRISPR/Cas9 can be successfully utilized to restore surface CTLA4 expression and function in human CD4+ T cells *in vitro* (outside a living organism) and in a CTLA4 knockout mouse model.

Highlight #2: CAR-T and HSC therapies

Research on gene therapies for the most severe primary immune deficiency diseases, such as various forms of Severe Combined Immunodeficiency (SCID), has been ongoing for the last few decades. Many proposed therapies for these diseases utilize chimeric antigen receptor (CAR)-T cells or hematopoietic stem cells (HSC) to aide in producing functional proteins to compensate for the genetic mutations causing the diseases. These therapies could both be theoretically translated to treat CTLA4 haploinsufficiency. Both techniques often require removal of the patient's own cells and manipulation of the cells ex vivo.

For CAR-T cell therapy, in the context of CTLA4 haploinsufficiency, regulatory T cells (Tregs) would be isolated from the patient's blood and genetically modified to produce functional CTLA4 by insertion of the corrected gene via a viral vector such as a gammaretroviral or lentiviral vector. These viruses are typically modified to remove pathogenic and replication components of the virus and insert the corrected form of the gene of interest (CTLA4, for instance), while leaving the mechanisms used by the virus to invade cells and produce the corrected protein (CTLA4) intact. The viral vectors enter the patient's cells and help to make functional versions of the mutated proteins. The cells are then infused back into the patient, who now possesses the corrected genes. HSC therapies similarly often utilize viral vectors for gene modification, but the use of stem cells corrects a mutation in all hematopoietic (blood-related) cells in the body, versus specific T cells in the lymphoid compartment, as achieved in CAR-T therapies.

While gene therapies may be on the horizon for treating individuals with CTLA4 haploinsufficiency, it is important for a patient to discuss the pros and cons of these therapies with their healthcare team to determine if a particular therapy is right for them. Gene therapy for CTLA4 haploinsufficiency could offer a long-term, sustainable treatment for this disease.

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For Patients, Family Members and Caregivers

Looking for resources on CTLA4 Haploinsufficiency?

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=CTLA4%20haploinsufficiency)
- Frontiers in Genome Editing, "Gene Edited T Cell Therapies for Inborn Errors of Immunity" (https://www.frontiersin.org/articles/10.3389/fgeed.2022.899294/full)
- Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/diseases/12316/autoimmune-lymphoproliferative-syndrome-due-to-ctla4-haploinsuffiency)
- Immune Deficiency Foundation (https://primaryimmune.org/)
- National Institute of Allergy and Infectious Diseases (https://www.niaid.nih.gov/diseases-conditions/ctla4-deficiency)
- The Journal of Allergy and Clinical Immunology, "The new quest in CTLA-4 insufficiency: How to immune modulate effectively?" (https://www.jacionline.org/article/S0091-6749(21)02601-4/fulltext)

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