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Crispr's Revolutionary Effects on Sickle Cell Disease

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ABSTRACT

CRISPR is a gene modifying tool that has a very promising future, especially in the field of biotechnology and medicine. CTX001 is an autologous, gene-modified stem cell that works by permitting as well as enabling the production of high levels of fetal hemoglobin. This is a type of CRISPR therapy utilized to treat hemoglobinopathies or diseases which result in abnormal hemoglobin structure, including sickle cell disease, a hereditary disorder that creates crescent-shaped red blood cells, which, as a result, causes dire consequences, that can be extremely painful as well as life-threatening. Currently, this therapy is facing ongoing trials in regards to treating sickle cell disease and transfusion-dependent beta-thalassemia (TDT), another inherited and genetic blood disorder, and further results and data are being observed and analyzed. The purpose of this research paper is to comprehend and recognize the value of CTX001 and its significance in regards to treating sickle cell disease as well as provide data and examples of patients who partook in the clinical trials of this CRISPR treatment, providing information on the effect of CTX001 on the disorder, and more importantly, their lives. Two patients were reviewed, providing details on different aspects such as personal experience as well as a more scientific data-oriented analysis. It was discovered, using these patients as primary examples, that so far, this treatment remains largely successful, increasing fetal hemoglobin production up to 40% and providing an increasing number of opportunities that people living with SCD can't imagine, including the absence of vaso-occlusive crisis episodes as well as eliminating the necessity of a transfusion, thus making life increasingly less painful.

Keywords: ***CRISPR, CTX001, Sickle Cell Disease, Vaso-occlusive episodes/VOC/Vaso-occlusive crisis, fetal hemoglobin***

Is CRISPR the solution to treat sickle cell disease, a debilitating disorder that plagues this world?

INTRODUCTION

Clustered regularly interspace short palindromic repeats, more commonly known as CRISPR, is a technological tool that grants the ability to alter, adapt and modify genes.[1] This impressive innovation was developed by two scientists, Emmanuelle Marie Carpenter and Jennifer Anne Doudna, who have recently procured the Nobel Prize in the field of Chemistry.[2] This creation targets and aims to edit deoxyribonucleic acid, or DNA, in an extremely precise manner.[3] Various instances where CRISPR proves to be revolutionary are gene therapies, diagnostics and therapeutics,[4] treating tremendously harmful diseases,[5] drug research, CRISPR-modified foods, as well as bioenergy. The more significant effects of CRISPR went far beyond prior gene-altercating tools. CRISPR has countless applications in numerous fields, including biotechnology, and medicine that could potentially transform the world of science and technology with the groundbreaking achievements that CRISPR unlocks, including treating sickle-cell disease, providing a wide range of possibilities in the future.

METHODS

By searching up phrases including "Sickle Cell Disease Treatment", "CRISPR patients", "CRISPR Research Papers", "Sickle Cell Disease CRISPR patients", and "Jimi Olaghere interview", multiple websites were visited. These websites were further explored, by verifying the reliability of these sources, namely identifying the certification and eligibility of the authors, surveying the goals of the organization, checking the publication dates, and the authenticity of the articles by being

reviewed. Furthermore, these websites provide important information about sickle cell disease, the therapy CTX001 and how it works on patients, specific patient experiences and more. Jimi Olaghere was then selected due to the immense amount of information provided about his experience in participating in the CRISPR trials. Another unnamed patient was included to delve into the scientific aspect of dealing with sickle cell disease and the results procured after partaking in the treatment.

CTX001 and its impact

Sickle cell disease is a debilitating disease. The red blood cells do not survive for a long period of time when diagnosed with sickle cell disease due to the abnormal shape of a crescent or sickle, thus leading to a scarce and inadequate amount of red blood cells, as a result, causing anemia. Furthermore, these sickle cells can get trapped in blood vessels, causing the blood to occlude.[6,7] This illness is a consequence of the mutated beta-globin production gene, a subunit of hemoglobin, required in order to carry oxygen. In recent years, ongoing trials for CRISPR-Cas9 test whether or not it is a viable method to treat this deadly and painful disorder.[8] One particular therapy, CTX001, made by CRISPR Therapeutics and Vertex Pharmaceuticals, reinstates the production of fetal hemoglobin.[9,10] This therapy works by extracting the patient's stem cells and collecting them through the blood, modifying them using CRISPR technology, to produce high levels of fetal hemoglobin, by deactivating the BCL11A gene (a switch that is turned on leading to the manufacture of adult hemoglobin and repression of fetal hemoglobin production).[11] The cells are reinstated, albeit modified, into the patient, with the new red blood cells produced containing fetal hemoglobin.[10]

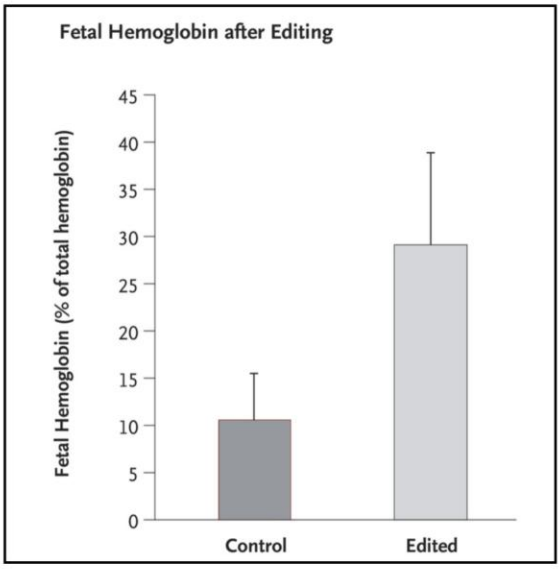

Figure displays fetal hemoglobin as a percentage before and after the modification process

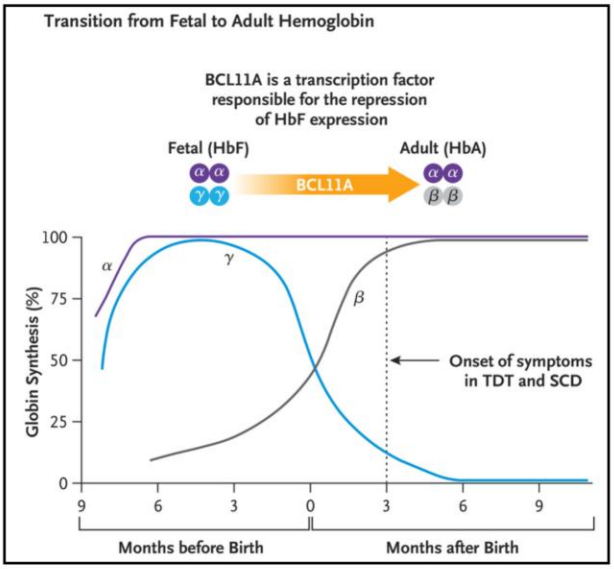

Figure displays the changes from fetal to adult hemoglobin in the span of a couple of months before and after birth

CLIMB-SCD-121 is the Phase 1/2 trials, in progress, in order to identify the effectiveness and success of one does of CTX001 in patients who are between 12 and 35 with severe SCD. Seven patients who participated all display alike responses, with quick and continual rises in the total as well as fetal hemoglobin present in the body. Furthermore, all were free of vast-occlusive crises after the infusion. According to previous data collected in 2021, after 4 to 26 months when CTX001 infusion occurred, improvements in total hemoglobin from 11 to 15.9 g/dL is seen as well as 39.6% to 49.6% of fetal hemoglobin present. Patients can participate if they had βS/βS or βS/β0 genotype and about 2 or more VOC's each year, 2 years prior.[12] Results show that CTX001 is capable of modifying the required gene in over 90% of hemopoietic stem cells as well as accomplish approximately 40% of fetal hemoglobin creation.[13]

RESULTS AND DISCUSSION

Jimi Olaghere partook in the CTX001 CRISPR trials for the treatment of sickle cell disease. A 36-year-old young man, Jimi lived with this debilitating disease since his early years, diagnosed at birth.[14] On Tuesdays, Jimi had appointments for IV

hydration. Once every fortnight, on Thursdays, blood transfusions were done in order to reduce the effects of anemia. Morphine was commonly administered to Jimi conductive to decreasing the painful crises, and was often admitted to the hospital due to the severity of his condition.[15] Living in Nigeria, as a young adult, further added to his difficulties, without being able to acquire emergency room access and suitable medication to handle the painful episodes of crises, sickle cell anemic patients face. This propelled him to relocate to the United States in order to reap the benefits of the advanced healthcare system present there.[14] Previously, for the sake of coping with the immeasurable pain, Jimi utilized hydroxyurea, originally employed for chronic myeloid leukemia (CML), and later also used for sickle cell disease as it aided in the increase in hemoglobin levels, and reduced painful episodes by approximately 50%.[16] However, after proving to be largely unsuccessful with two attempts, Jimi put an end to this treatment. Jimi's family persuaded him into searching for a long-term solution. After exploring bone marrow and stem cell transplants, Jimi stumbled across gene editing. He received an NPR alert regarding a trial that occurred in the United States, previously tested on a person, Victoria Gray, which appeared to work for her thus far.[14] He viewed an article regarding a clinical trial for treating SCD with gene editing.[17] Dr. Haydar Frangoul, head researcher for the trial of CRISPR-Cas9 for Sickle Cell Disease ß- Thalassemia cleared Jimi as a suitable person to participate in this trial.[14] Jimi's bone marrow stem cells were collected in January 2020, and over the period of the next six months, this was done another three more times.[15] The treatment worked by extricating the stem cells that could lead to producing sickle-shaped red blood cells, followed by genetically modifying those cells using CRISPR by a team of scientists. The BCL11A gene is switched off. Furthermore, Jimi was to go through a round of chemotherapy for the destruction of the cells producing the sickle cells. Next, these modified cells were given to Jimi, which can now produce healthy fetal hemoglobin as well as ordinary red blood cells.[17] During the time period between the DNA collection and the cell manufacturing to the time after the transplant, Jimi was required to remain in the hospital and medical apartment for approximately three months before he was discharged. While the experience was burdensome and tough, the overall results outweighed the problems he faced. This form of therapy enabled Jimi to engage in activities, previously too arduous to take part in. Before, recovery after traveling was necessary due to swollen ankles, incapacitating Jimi for up to two weeks, and preventing him from even performing the simple task of walking. Now, however, no rehabilitation time is needed. Furthermore, Jimi had to avoid cold weather as it triggered a crisis, which is no longer required after therapy.[14]

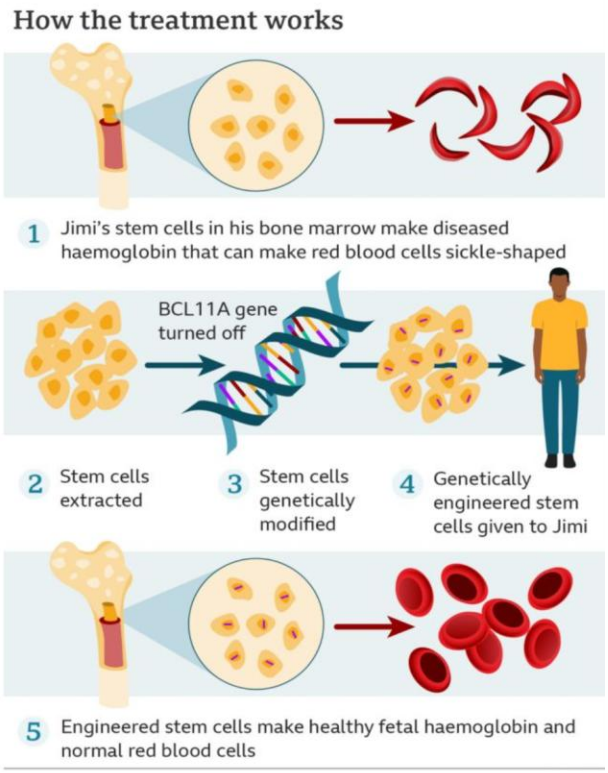

Figure displays CTX001 treatment process of the patient Jimi Olaghere and how it was carried out

This patient is a 33-year-old young women who has sickle cell disease. It has been documented and observed that in the two years prior to her participation in this trial, she had about seven serious vaso-occlusive episodes a year. Furthermore, she had 3.5 enrollment to hospitals in regards to SCD as well as 5 red blood cell transfusions each year. She suffered from cholelithiasis, continuous pain, lowered haptoglobin levels as well as high lactic dehydrogenase levels.[18] Myeloablative conditioning, done to destroy the hematopoietic stem cells in the bone marrow,[19] and CTX001 infusion occurred. This infusion took place over two manufacturing lots. Her hemoglobin level rose from 7.2 g/dL to 10.1 g/dL and 12 g/dL, 3 and 15 months later respectively.[18] Moreover, data presents that the fetal hemoglobin level increased. Initially, it was at 9.1%, with sickle hemoglobin at 74.1%. When checked 3 months later, fetal hemoglobin reached to37.2% and sickle hemoglobin level reduced to 32.6%. However, 15 months after the infusion, both fetal and sickle hemoglobin levels increased to 43.2% and 52.3% accordingly. 3 adverse events which were categorized as serious occurred, neutropenic sepsis on day 16, cholelithiasis on day 49 and abdominal pain on day 56. Additionally, it was observed that no VOC's occurred in the 16 months after CTX001 infusion. Lymphopenia was also discerned and was allocated as a non-serious adverse event. The results of this patient display the extent of the successfulness of the treatment, with high levels of fetal hemoglobin, the absence of VOC's and the eradication of the requirement for transfusion.[18]

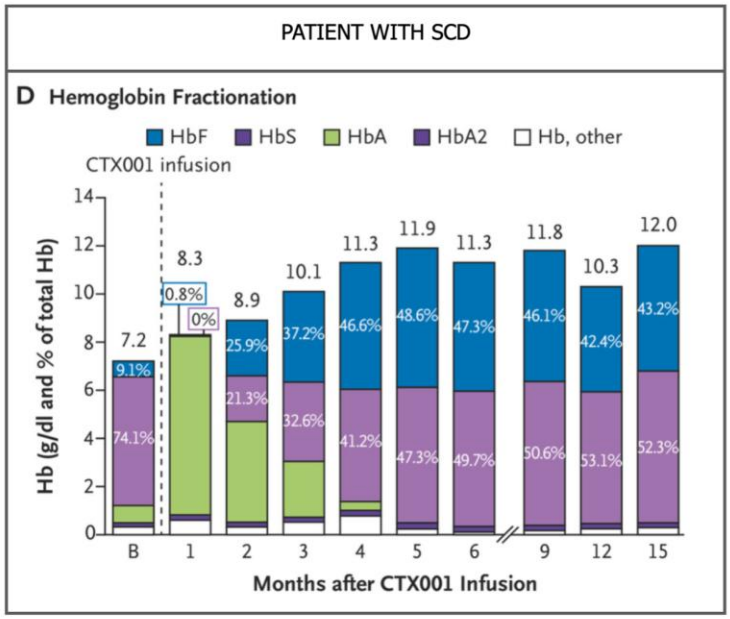

Figure displays blood divisions in patient over the span of 15 months

CRISPR therapy CTX001 therefore presents groundbreaking feats in the treatment of sickle cell disease, reducing or removing the need for transfusion, eliminating vaso-occlusive crisis, and thus the pain that accompanies it as well as present high levels of fetal hemoglobin. Therefore, in conclusion, the findings that were discovered of the two patients match the thesis of the unprecedented achievements of CRISPR in regards to treating SCD.

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