

Sickle Cell Anemia: Finding the Right Cure

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Sickle cell Anemia is a debilitating genetic mutagenic disease that affects 100,000 people worldwide. Several breakthroughs have been made through the advancement of technology and science. Blood transfusions, current medication, and fetal hemoglobin have been discovered to help with the symptoms. Bone marrow transplants and the use of stem cells have cured people but are of high risk because of infection or incompatibility. A definitive cure with little or no risk is necessary to combat this disease in a grandiose way. Granted, there have been people cured but the current treatments are not safe and reliable. Encouraging recent breakthroughs have been made in the area of gene therapy but just like any new experimental procedure protocol must be followed to bring it into fruition. Ultimately, gene therapy is going to be the permanent cure fixing the problem at the source.

Introduction

Sickle cell disease is a recessive genetic (point-shift) mutation causing the genetic coding of the amino acid valine in the place of the number six amino acid glutamic acid in the beta hemoglobin chain. Normal hemoglobin has two alpha hemoglobin chains and two beta hemoglobin chains, sickle cell causes hemoglobin S (Bender, 2003). This gives the blood cells their characteristic cyclical shape. Normal red blood cells are elastic and strong but sickle cells are brittle and the outer membrane adheres more to the endothelium. The life span of normal red blood cells is four months while the life span of the abnormal-sickle blood cell is only four weeks. This misshapen blood cell can cause a variety of symptoms. Abnormal blood cells are more susceptible to hemolytic conditions and cause vascular occlusion. Occlusion can cause swelling in the extremities and decreased blood flow to the brain, chronic or acute pain throughout the body, and organ damage. Young infants can have engorgement of the spleen causing them to become more susceptible to certain types of bacterial infection. With long term hemolysis, children can suffer throughout their development: low red blood cell count (anemia), dysfunctional liver (jaundice), cholelithiasis, and delayed growth and sexual maturity (Bender, 2003). Many steps have been taken through advanced science in

progression towards finding a cure by first identifying the protein responsible for regulation of fetal and adult hemoglobin and also genes responsible for coding the hemoglobin protein. New breakthroughs in the area of gene therapy and stem cells have been discovered. There are a variety of treatment options; both experimental and common, and some people have been cured. However, most of these treatment options have a variety of problems. Some mask the problem by not really fixing the genetic mutation but giving someone the ability to live a little more comfortable. Other treatments are risky and have paid off for certain people but not necessarily good viable options for the general populace.

Short term treatments are repetitive and only provide a patch against the treatment of this debilitating disease. People with sickle cell disease have to be treated through blood transfusion on a repetitive basis. The problem with this treatment is blood serum must be monitored for iron concentration because of the tendency for elevation. Along with blood transfusion is the common treatment of Hydroxyurea medication. This medication is somewhat effective in decreasing the sickling of blood cells and increasing cell survival. It also has increased the dilation of blood vessels causing less occlusive episodes which leads to less pain in the

extremities and elsewhere (Bender, 2003). However, there are other side effects and does not treat the disease.

A new advancement in the area of treating patients was the discovery of a hemoglobin- regulating protein called BCL11a. In 2007 the National Institute of Health-funded scientists discovered decreasing BCL11a production causes suppression of adult hemoglobin and increase of fetal hemoglobin. Fetal hemoglobin enables red blood (tested on rat with disease) infected with SCD to produce more normal red blood cells. Fetal hemoglobin is turned off after the first year of development and adult hemoglobin begins production in humans. By shutting down production through genetic alteration of erythroid progenitor cells, scientists caused an increase in the production of fetal hemoglobin. The increase in fetal hemoglobin and decrease in adult hemoglobin cause normal formation of blood cells (ASH, 2012). Currently, there are scientists working on development of a drug that will inhibit the production of BCL11A protein or adult hemoglobin production. However, medicine or treatment is still a long ways out from being a viable option for the general populace. Extensive testing and protocol must be followed to prove this to be a viable option.

Bone marrow transplantation is another viable option that has cured people. By bringing in bone marrow from a healthy relative, the infected patient with the incorporated bone marrow will produce healthy red blood cells. However, this option can cause complications. Many people have died due to the complications associated with transplantation. Like any organ being transplanted, a perfect match of the same tissue types must be made between the donor and patient in order for the immune system to not reject the bone marrow. This usually involves the use of the patient's sibling or other healthy relative. Only twenty percent of patients have a sibling whose tissue type will match the patient (Weiss, 2007). Even if the tissue type matches and there is no immunological response from the patient, there is the susceptibility of infection associated with transplantation. Another option would be stem cell transplantation. The stem cell option is sort of a last stitch effort when other options have not been successful because of the high rate of morbidity. Morbidity can be caused from a variety of problems. It could be from infection; but it most commonly happens with cerebrovascular events. The problem with this option is again finding a suitable donor who has the right sib stem cells (Bender, 2003).

Recent Progress

There has been extensive advancement in the area of stem cells however through the development of iPS cells. The advantage of using iPS cells is that these cells are created from one's own body and are identical in nature. The

problem with using a donor cells all along is that the glycocalyx layers of the donor and patient cells are different and this signals the body's immunological response to take effect to destroy the foreign cells. To combat this problem doctors have come up with medications to shut down the immune response. The disadvantage to having a lowered immune system is the susceptibility to infection. With iPS cells, this is a thing of the past. Scientists have been able to cure mice with sickle cell anemia using skin cells from the mice tails of the infected mice altering them to become undifferentiated iPS cells. This is done through infecting these cells with an engineered virus containing the genetic code that shuts down cell specificity and allows the cell to revert back to an undifferentiated state. The scientists were able to take out the small mutation that causes sickle cell disease and place in the proper genetic code by using DNA splicing techniques. Then they were able to implement differentiation in these cells through a viral vector and were able to make them bone marrow cells. This was then given back to the mice via a bone marrow graft. The healthy cells containing the proper genetic code began to produce healthy normal red blood cells. Because the cells were the identical genetic makeup of the individual, it results in less downtime for the patient and a better recovery (Weiss, 2007).

However, gene therapy is a long way away from being perfected. X-CID trials in France proved that gene therapy was promising; but nevertheless, not a fool proof fix. Although 9 out of 10 patients were cured of their disease, there is a problem with development of leukemia through insertional mutagenesis (Arthor, 2008). Four of the ten patients have developed this leukemia. They were able to isolate the cause of the problem. The problem was an activation of LMO2 which caused an emergence of a proliferative leukemic clone. This activation was done by a retroviral promoter enhancer near the known oncogene LM02. They have since changed to lentiglobin vectors to prevent the manifestation of Leukemia (Arthor, 2008).

Discussion

In conclusion, what better way to treat a disease than to cure it at the problem? Organ and tissue damage, anemia, chronic and widespread pain associated with sickle cell disease is not the problem. The problem is in the genetics and gene therapy shows the most promise compared to the other treatments that just mask the symptoms. It was because of the many physiological discoveries and matching gene to functional discoveries that scientists have been able to make the progress in finding a cure for sickle cell disease. Hemoglobin protein was one of the first proteins to be mapped out using x-ray crystallography by Muirhead H, Perutz MF and ironically the very protein that is mutated in people affected by

sickle cell disease. There has been people cured along the way of discovery but there hasn't been a definitive cure that will work for the general populace. I believe that gene therapy is going to provide the best solution to this debilitating problem that affects over 100,000 people worldwide. Gene therapy is going to provide the most reliable cure for this disease by first tackling the incorrect mutated sequence and placing in the correct sequence of nucleic acids that will ultimately produce the right hemoglobin. Once perfected, Gene therapy could ultimately fix a vast array of other genetic blood disorders as well.

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