EDITORIAL

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Gene therapy in sickle cell disease: Possible utility and impact

In developed countries, 95% of children with sickle cell disease (SCD) survive into adulthood, yet the median age of death remains in the mid-40s,[1] highlighting the clear need for curative therapies for this disease.

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At present, the only potentially curative option is allogeneic stem cell transplant (ie, bone marrow transplant), which requires human leukocyte antigen (HLA) matching of a suitable healthy donor. But a lack of donors, the risk of graft-vs-host disease and graft failure, and long-term toxicities related to pretransplant conditioning regimens are major drawbacks.

Gene therapy may provide an option for SCD patients without a suitable bone marrow donor. However, questions remain as to its cost, its long-term efficacy, and whether it can be done with less-toxic conditioning regimens.

CRISPR-Cas9 makes it possible to edit the patient's own genes

THE ONGOING CHALLENGES OF BONE MARROW TRANSPLANT

HLA-matched sibling donor transplants have a 5-year overall survival rate of 95% for children under age 16 and 81% for those age 16 and older, with a 5-year graft-vs-host disease-free survival rate of 86% for those under age 16 and 77% for those age 16 and older.[2]

The timing of bone marrow transplant plays an important role in the chance of overall success, as each additional year of delay increases the hazard ratio of death by 10%.

Only 18% of people with SCD have an HLA-matched sibling who does not have SCD. Other patients have to rely on the unrelated-donor registry to find a suitable HLA match, but only 16% to 18% of African Americans have a full HLA-matched unrelated donor option in the national donor pool, and unrelated donor transplants are associated with a higher rate of graft-vs-host disease than HLA-matched sibling donor transplants.[3]

To meet these challenges, the donor pool has been expanded to include partial-matched healthy unrelated, half-matched (ie, haploidentical) donors, and partial-matched cord blood units as options when a suitable sibling or full-match donor is not available. However, these options carry increased risk of graft-vs-host disease and graft failure.[4]

Another challenge is that bone marrow transplant requires conditioning chemotherapy to destroy the recipient's bone marrow before the infusion of healthy donor cells. Previously, for patients with SCD, transplant was preceded by myeloablative conditioning with high-dose chemotherapy and radiotherapy, which was associated with immediate and long-term complications including transplant-related infertility and death. More recently, regimens using reduced-intensity or nonmyeloablative conditioning are being used and have decreased the risks of immediate and long-term complications, with success rates similar to those for matched-sibling donor transplant for SCD. A similar approach is being evaluated in a study of unrelated-match donor grafts.[5]

In summary, while advances in allogeneic bone marrow transplant offer higher rates of survival and disease cure, the procedure still has the serious limitations of the lack of suitable donors, the risk of graft-vs-host disease and graft rejection associated with use of related or unrelated partial-matched donors, and long-term adverse effects of myeloablative conditioning.

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GENE THERAPY

Gene therapy is emerging as a second curative option for SCD, apart from allogeneic bone marrow transplant. Marrow cells are removed, genetically modified, and then reinserted into the patient, mitigating the risk that the gene modification could affect other somatic or germline cells.

The new gene is inserted by using lentivirus vectors or by using clustered regularly interspaced short palindromic repeats (CRISPR). In the lentivirus vector approach, new genetic material is inserted into a cell's DNA, causing the altered cell to replicate and express the new gene. In CRISPR therapy, short palindromic DNA repeats are recognized by an enzyme called Cas9, which then removes those sequences from the DNA.[6] Then, during the DNA repair process, new corrected sequences are added, resulting in normal genetic function.

Gene therapy does not correct the genetic mutation that causes SCD; instead, it adds additional genes or modifies the regulation of other genes. A variety of genes are being added or altered in gene therapy studies for the treatment of SCD to prevent hemoglobin sickling, to add a beta-hemoglobin gene, or to induce the production of hemoglobin F.[7]

Major advantages of gene therapy are that it uses the patient's own cells, eliminating the need for an HLA-matched donor and the risk of graft-vs-host disease. But myeloablative conditioning is still required so that the genetically modified stem cells are not rejected by the patient's own marrow. Studies are examining the possiblity of less toxic conditioning regimens.[8]

Most studies of gene therapy for SCD are in early phases with short follow-up times, and questions about gene persistence and potential long-term toxicities are as yet unanswered.[7] Further, many of the outcomes targeted by current gene therapy trials are reproducible without gene therapy: hydroxyurea increases hemoglobin F, the oral agent voxelotor reduces sickling, and blood transfusion adds normal hemoglobin. And although these treatments can improve disease status, they are not curative.[9] Even though gene therapy also offers a curative option for SCD, we need to see its long-term persistence and effectiveness. A key advantage of gene therapy is that it can achieve these outcomes with a one-time treatment instead of requiring a lifetime of medication or transfusions.

GENE THERAPY IN SCD: THE BOTTOM LINE

In SCD, gene therapy may prove to be a good option for those without an HLA-matched donor. On the other hand, gene therapy still requires a toxic conditioning regimen, and the long-term efficacy is not yet known. Finally, the cost of this curative gene therapy option is still unknown. Most would agree that a one-time curative option with a hefty price tag may be a good option compared with continuous lifelong management of a chronic disease. However, it is still unclear how expensive gene therapy will be, and whether it will be available to those not living in developed countries.

There is a need for more curative therapies for SCD other than allogeneic bone marrow transplant for patients with a suitable donor option, and gene therapy may provide a good curative option for those who do not have a suitable bone marrow donor. However, questions remain as to the affordability and the long-term efficacy of gene therapy, and whether it can be done with less toxic conditioning regimens.

Questions remain about cost, long-term efficacy, and less toxic conditioning regimens

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