EDITORIALS

Gene Therapy as a Curative Option for β-Thalassemia

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With an estimated global prevalence of 288,000 cases, β-thalassemia is one of the most common genetic diseases in the world, and every year another 60,000 infants are born with the disease. Of these patients, 60 to 80% have a severe form of the disease and require regular red-cell transfusions and iron chelation for proper treatment of disease manifestations. In the United States and the European Union, the prevalence is estimated to be 15,000, with approximately 1500 infants born each year with the disease. However, in North Africa, the Middle East, and Asia, β-thalassemia is more prevalent. In many of these regions, patients have limited access to the most effective treatments and thus are at increased risk for substantial organ dysfunction at an early age.[1,2]

The need for a curative treatment for transfusion-dependent β-thalassemia can be addressed with allogeneic transplantation of hematopoietic cells. The transplantation of such cells obtained from a matched sibling donor results in a rate of disease-free survival of more than 90% among pediatric β-thalassemia patients with a low disease burden at the time of transplantation.[3,4] Adults with β-thalassemia and patients receiving transplants from an unrelated or alternative donor have a less favorable prognosis.[3,4] Now, gene therapy could be on the way to becoming an alternative curative treatment for β-thalassemia in many patients, including those who lack a matched sibling donor.

In 2010, Cavazzana-Calvo and colleagues[5] reported the first successful use of gene therapy for the treatment of β-thalassemia in a patient with a β^{E}/β^{0} mutation, a genotype that affects approximately half of all patients with transfusion-dependent β-thalassemia worldwide. The patient received an infusion of autologous hematopoietic stem cells (HSCs) that had been transduced ex vivo with a lentiviral vector carrying an extended β-globin gene structure for β-chain gene replacement. The vector was administered after the patient had undergone a myeloablative conditioning regimen. After engraftment of the engineered HSCs, a progressive increase of transgenic hemoglobin synthesis was observed, which led to stabilization of the patient's overall hemoglobin value at levels that rendered him transfusion-independent for up to 6 years after treatment. However, transduced-cell engraftment was associated with a transient clonal expansion of erythroid cells, with the vector insertion site at the *HMGA2* locus. Such clonal expansions are typically followed closely to determine whether they are harbingers of possible adverse events.

In this issue of the *Journal*, Thompson and colleagues[6] report the interim results of two companion phase 1/2 studies conducted in the United States and France that evaluated the safety and efficacy of gene therapy for β-thalassemia with the use of a lentiviral vector[7] derived from the first vector administered to the original patient.[5] The 22 patients who were treated in the two studies were monitored for a maximum of 42 months after transplantation. Nine of the patients had a β^{0}/β^{0} genotype, a severe form of the disease that results in microcytic, hypochromic anemia. In this expanded patient cohort, engraftment of engineered HSCs resulted in a progressive increase in transgenic hemoglobin synthesis and stabilization of the patients' overall hemoglobin values at levels that rendered them transfusion-independent or allowed a robust

reduction in their transfusion requirements. Indeed, all the patients with a β^E/β^0 genotype were able to discontinue transfusions, and those with a β^0/β^0 genotype saw a 73% reduction in their transfusion volume and a 74% reduction in the annual number of transfusions, with 3 patients later becoming transfusion-independent. These results are of great importance, considering the widespread prevalence of the β^E/β^0 genotype and the major effect of reducing the transfusion needs of patients with the β^0/β^0 genotype on their overall quality of life and long-term prognosis. Notably, therapeutic efficacy was safely achieved in the absence of treatment-related adverse events or clonal expansions at the latest follow-up.

Several factors could have contributed to this favorable outcome, including the availability of a large number of engraftable HSCs after gene transfer, the high quality of the clinical-grade vector preparations, and the robust transduction efficiency achieved in the medicinal product. As these exciting results certainly set the stage for future development of HSC gene therapy as a curative treatment for β-thalassemia, they also highlight critical determinants of benefit to be considered as investigators plan to scale up this therapy for wider application. These factors include the availability of adequate starting material (autologous HSCs and clinical-grade vector in appropriate quantity and of high quality) and of a proper manufacturing capability for the transduced cells.

Recent progress in gene therapy has been made by targeting discrete groups of patients with certain immunodeficiencies and hemophilia. β-thalassemia is one of the first examples in which gene therapy could be applied to a large population of patients who reside mostly in developing countries. Thus, the large-scale feasibility and cost management of this potentially curative treatment, as well as of the other gene therapies being developed for β-thalassemia (ClinicalTrials.gov numbers, NCT01639690, NCT02453477, and NCT03432364), present exciting challenges for the gene-therapy community.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Managing the Most Precious Resource in Medicine

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Many health care institutions appear to have lost sight of the truism that our health professionals are our most precious resource. With increasing commoditization, commercialization, productivity targets, and administrative burdens, the volunteerism and soul that have typified our profession for generations are suffering. It is increasingly clear that many residents and physicians are focused on surviving rather than thriving. The residents who participated in the iCOMPARE (Individualized Comparative Effectiveness of Models Optimizing Patient Safety and Resident Education) trial,[1] reported now in the *Journal*, may provide the clearest signal yet of the distress they feel and may also help us identify the way forward.