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CRITICAL REVIEW OF: “GENE THERAPY IN PATIENTS WITH TRANSFUSION-DEPENDENT β-THALASSEMIA”


These interim results of 2 phase I/II trials are remarkable. Thompson and colleagues demonstrate the progress of clinical gene therapy for monogenetic diseases with a median observation time of 26 months. With a further reduction in transplant-associated morbidity using less intensive conditioning, this potentially curative treatment of beta-thalassemia might become standard of care in the future not limited to high-income countries. However, long-term follow-up data are still needed.

JOSHA’S Conclusion:

IMPORTANT PROGRESS – MAY BE APPLIED AS STANDARD OF CARE FOR SELECTED PATIENTS,

Original Article

“Gene Therapy in Patients with Transfusion-Dependent βThalassemia”

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Authors


Original Abstract

Background

Donor availability and transplantation-related risks limit the broad use of allogeneic hematopoietic-cell transplantation in patients with transfusion-dependent β-thalassemia. After previously establishing that lentiviral transfer of a marked β-globin (βA-T87Q) gene could
substitute for long-term red-cell transfusions in a patient with β-thalassemia, we wanted to evaluate the safety and efficacy of such gene therapy in patients with transfusion-dependent β-thalassemia.

**Methods**

In two phase 1–2 studies, we obtained mobilized autologous CD34+ cells from 22 patients (12 to 35 years of age) with transfusion-dependent β-thalassemia and transduced the cells ex vivo with LentiGlobin BB305 vector, which encodes adult hemoglobin (HbA) with a T87Q amino acid substitution (HbAT87Q). The cells were then reinfused after the patients had undergone myeloablative busulfan conditioning. We subsequently monitored adverse events, vector integration, and levels of replication-competent lentivirus. Efficacy assessments included levels of total hemoglobin and HbAT87Q, transfusion requirements, and average vector copy number.

**Results**

At a median of 26 months (range, 15 to 42) after infusion of the gene-modified cells, all but 1 of the 13 patients who had a non–β0/β0 genotype had stopped receiving red-cell transfusions; the levels of HbAT87Q ranged from 3.4 to 10.0 g per deciliter, and the levels of total hemoglobin ranged from 8.2 to 13.7 g per deciliter. Correction of biologic markers of dyserythropoiesis was achieved in evaluated patients with hemoglobin levels near normal ranges. In 9 patients with a β0/β0 genotype or two copies of the IVS1-110 mutation, the median annualized transfusion volume was decreased by 73%, and red-cell transfusions were discontinued in 3 patients. Treatment-related adverse events were typical of those associated with autologous stem-cell transplantation. No clonal dominance related to vector integration was observed.

**Conclusions**

Gene therapy with autologous CD34+ cells transduced with the BB305 vector reduced or eliminated the need for long-term red-cell transfusions in 22 patients with severe β-thalassemia without serious adverse events related to the drug product. (Funded by Bluebird Bio and others; HGB204 and HGB-205 ClinicalTrials.gov numbers, NCT01745120 and NCT02151526.)

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JOSHA’S Critical Reviews in Oncology and related areas of medicine and science will focus on recently published clinical and non-clinical studies and discoveries. Our editors feel that there is a strong need for expert opinions on studies and discoveries that may potentially impact on patient care. While any judgment will, of course, be a personal and subjective opinion of our editors with all its limitations, we do hope this service will be helpful for our readers and stimulate thoughts and reflections in face of ever more rapid introductions of new drugs and therapeutic strategies in these days. Our editors will address these questions: What is the benefit for the patient? focusing on therapeutic responses, side effects and quality of life. They will also address the risk-benefit ratio and the cost-benefit ratio. Reviews are kept short and concise and conclusions are categorized using following tiers:

• IMPORTANT PROGRESS – A true step forward that may be applied as the standard of care
• MODERATE PROGRESS – May be applied after a critical review of alternatives
• UNCERTAIN PROGRESS – Not to be applied except under special circumstances
• NO PROGRESS – Not to be applied. We do encourage comments by our readers!