JOSHA'S CRITICAL REVIEW OF "GENE THERAPY IN PATIENTS WITH TRANSFUSION-DEPENDENT β-THALASSEMIA" BY A.A. Thompson et al. N Engl J Med 2018; 378:1479- 1493.

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

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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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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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• 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!