**Lentiviral Vector-Based Gene Therapy Eliminates the Need for Red-cell Transfusion in Patients With β-Thalassemia Major.**

Lentiviral vector-based gene therapy eliminates the long-term need for red-cell transfusion in patients with transfusion-dependent β-thalassemia with non-$\beta^0/\beta^0$ genotype.

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April 25, 2018 – In patients with non-$\beta^0/\beta^0$ genotype transfusion-dependent β-thalassemia, CD34+ cells transfused with a lentiviral vector encoding modified hemoglobin (LentiGlobin BB305) eliminated the need for long-term red-cell transfusion, a single-dose open-label showed.

Alexis A. Thompson, MD, MPH, with the Ann and Robert H. Lurie Children's Hospital of Chicago, reported the cumulative findings of 2 phase 1/2 studies in the April 19, 2018 issue of *The New England Journal of Medicine.*

Lifelong transfusion of red blood cells with iron chelation is the standard care for patients with transfusion-dependent β-thalassemia (TDBT). Despite efforts to minimize complications and improve the standard of care, blood transfusion-associated infections and toxicity present a considerable risk and hinder disease management.

LentiGlobin BB305 is a lentiviral vector that encodes adult hemoglobin with a single amino acid substitution ($HbA^{T87Q}$). In this nonrandomized study, the researchers evaluated the efficacy of LentiGlobin BB305 to correct hemoglobin synthesis in patients with TDBT.

A total of 22 patients (12-35 years) with TDBT were enrolled in this study. Mobilized autologous CD34+ hematopoietic stem cells (HSCs) were harvested from each patient and transduced ex vivo with LentiGlobin BB305 vector.

For myeloablative conditioning, patients received busulfan intravenously for 4 consecutive days. The initial dose was 3.2 mg/kg/day and was adjusted based on the daily pharmacokinetic analysis. The patients received an intravenous dose of transduced CD34+ HSCs ($\geq 3 \times 10^6$ cells/kg) 7 days post-myeloablative conditioning.

The efficacy endpoints were quantification of vector-derived $HbA^{T87Q}$ in the peripheral blood and discontinuation of red blood cell transfusions. Safety endpoints included: overall survival, frequency and severity of adverse events, rate of transplantation-related death at 100 days, hematopoietic engraftments and kinetics, vector-derived replication-competent lentivirus detection and vector integration site analysis.

The investigators reported that, although not by design, the "clinical outcomes appeared to vary according to the underlying genotype."

Of the 13 patients with non-$\beta^0/\beta^0$ genotype, 12 discontinued red-cell transfusions at a median follow-up of 26 months. The median levels of vector-derived $HbA^{T87Q}$ and total hemoglobin levels were 6 g/dL (range, 3.4 -10 g/dL) and 11.2 g/dL (range, 8.2-13.7 g/dL) respectively.

Of the 9 patients with $\beta^0/\beta^0$ genotype or IVS1-110 mutation homozygosity, 3 stopped receiving blood transfusions. In the remaining 6 patients, a 74% median reduction in the number of transfusions (range, 7%-100%) and 73% lower transfusion volumes (range, 19%-100%) was observed.

The adverse effects noted were attributed to busulfan conditioning, and no safety issues related to the vector was reported.

Dr Thomson and colleagues acknowledged that "The number of patients who were treated remains relatively small, so extended follow-up is required to establish the durability of transduction hematopoietic stem cells and progenitor cells after a single infusion."

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Thompson AA, Walters MC, Kwiatkowski J, et. al. Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia. *N Engl J Med*. 2018 Apr; 378(16):1479-1493