

X-SCID GENE THERAPY TRIAL Update

“Gene Transfer for SCID-X1 using a self-inactivating (SIN) gammaretroviral vector”

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Clinicaltrials.gov NCT01129544

Dear Colleagues,

We want to update you on a recent amendment we have made to our **Gene Transfer for SCID-X1 using a self-inactivating (SIN) gammaretroviral vector** protocol. Based on experience in other transplant and gene therapy trials, we have now modified the protocol to include low dose Busulfan conditioning in patients without active infections, in order to enhance correction of humoral (B cell) immunity. The trial is currently open and enrolling. This trial is being performed as a collaboration among U.S. sites at Children's Hospital Boston, Cincinnati Children's, and Mattel Children's Hospital (UCLA), and the Great Ormond Street Hospital in London.

To date we have enrolled and treated 7 patients in the United States and 6 patients in Europe. An interim analysis of the study was published in the New England Journal of Medicine in October 2014. (Hacein-Bey-Abina S, Pai S-Y, Gaspar HB, et al. A Modified γ -Retrovirus Vector for X-Linked Severe Combined Immunodeficiency. N Engl J Med. 2014 Oct 9;371(15):1407–17.) There have been no serious adverse effects related to the gene therapy medicinal product to date in this trial.

All research aspects of the protocol will be paid for patients treated in the U.S. through a grant from the NIAID, NIH. Reimbursement for clinical costs will be sought from third party payors.

Major Eligibility Criteria:

INCLUSION

1. Diagnosis of SCID X1: < 200 autologous CD3+ T cells
2. Molecular confirmation of IL2R γ defect
3. Lacking HLA identical related donor
4. In good clinical condition without a readily available 10/10 HLA identical unrelated donor OR

Patient without an HLA identical related donor with an active, therapy-resistant infection or other condition which significantly increases risk of HCT

EXCLUSION

1. Lack of molecular diagnosis of SCID-X1
2. Has HLA identical related donor
3. Has malignancy (except for EBV-LPD)
4. HIV-1 infected
5. Previous gene transfer
6. Life-threatening congenital anomaly

Contacts

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A modified γ -retrovirus vector for X-linked severe combined immunodeficiency.

Hacein-Bey-Abina S1, Pai SY, Gaspar HB, Armant M, Berry CC, Blanche S, Bleesing J, Blondeau J, de Boer H, Buckland KF, Caccavelli L, Cros G, De Oliveira S, Fernández KS, Guo D, Harris CE, Hopkins G, Lehmann LE, Lim A, London WB, van der Loo JC, Malani N, Male F, Malik P, Marinovic MA, McNicol AM, Moshous D, Neven B, Oleastro M, Picard C, Ritz J, Rivat C, Schambach A, Shaw KL, Sherman EA, Silberstein LE, Six E, Touzot F, Tsytsykova A, Xu-Bayford J, Baum C, Bushman FD, Fischer A, Kohn DB, Filipovich AH, Notarangelo LD, Cavazzana M, Williams DA, Thrasher AJ.

Abstract

BACKGROUND:

In previous clinical trials involving children with X-linked severe combined immunodeficiency (SCID-X1), a Moloney murine leukemia virus-based γ -retrovirus vector expressing interleukin-2 receptor γ -chain (γ c) complementary DNA successfully restored immunity in most patients but resulted in vector-induced leukemia through enhancer-mediated mutagenesis in 25% of patients. We assessed the efficacy and safety of a self-inactivating retrovirus for the treatment of SCID-X1.

METHODS:

We enrolled nine boys with SCID-X1 in parallel trials in Europe and the United States to evaluate treatment with a self-inactivating (SIN) γ -retrovirus vector containing deletions in viral enhancer sequences expressing γ c (SIN- γ c).

RESULTS:

All patients received bone marrow-derived CD34+ cells transduced with the SIN- γ c vector, without preparative conditioning. After 12.1 to 38.7 months of follow-up, eight of the nine children were still alive. One patient died from an overwhelming adenoviral infection before reconstitution with genetically modified T cells. Of the remaining eight patients, seven had recovery of peripheral-blood T cells that were functional and led to resolution of infections. The patients remained healthy thereafter. The kinetics of CD3+ T-cell recovery was not significantly different from that observed in previous trials. Assessment of insertion sites in peripheral blood from patients in the current trial as compared with those in previous trials revealed significantly less clustering of insertion sites within LMO2, MECOM, and other lymphoid proto-oncogenes in our patients.

CONCLUSIONS:

This modified γ -retrovirus vector was found to retain efficacy in the treatment of SCID-X1. The long-term effect of this therapy on leukemogenesis remains unknown. (Funded by the National Institutes of Health and others; ClinicalTrials.gov numbers, NCT01410019, NCT01175239, and NCT01129544.).

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