Interim Results from a Phase I/II Clinical Gene Therapy Study for Newly Diagnosed Infants with X-Linked Severe Combined Immunodeficiency Using a Safety-Modified Lentiviral Vector and Targeted Reduced Exposure to Busulfan

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Funding Grants: Lentiviral Gene Therapy for Infants with X-linked Severe Combined Immunodeficiency using Autologous Bone Marrow Stem Cells and Busulfan Conditioning

Public Summary:
X-linked Severe Combined Immunodeficiency (X-SCID) is a life-threatening disease that affects young children who are born without a functioning immune system. As a result, they will die from overwhelming infections in the few years of life if not treated quickly with some form of therapy that fully restores their immune system. Bone marrow transplant has been used for this purpose, but is only maximally effective in half of the cases where a matched brother or sister can serve as a bone marrow donor. For the other patients, various experimental therapies have been tested including gene therapy, where a normal copy of the X-SCID gene is inserted into the patient’s own bone marrow stem cells. Early results with gene therapy have resulted in a high incidence of leukemia due to the procedure. Later gene therapy trials appear safer but only correct a subset of the immune defects that cause X-SCID. In particular, gene therapy has not been successful in restoring antibody production in the patients, so that they remain dependent of regular and expensive injections of human antibodies for the remainder of their life. In this CIRM-sponsored gene therapy trial, we have tested a new method for performing gene therapy in X-SCID infants that uses for the first time a chemotherapy drug called busulfan to increase the number of corrected bone marrow cells after gene therapy. The busulfan is given at a low dose and is monitored in every patient to achieve tight control of dosing and to avoid toxicity. The other unique aspect is that we use a lentiviral vector to transfer the normal copy of the X-SCID gene to the patient. The lentiviral vector is both safer in terms of not causing leukemia and is more efficient at transferring the therapeutic gene. To date, we have treated 7 patients with this technique and have noted robust immune correction in all cases, including correction of antibody production allowing us to stop antibody replacement therapy in 3 cases to date. Other immune functions have also normalized, these children have cleared pre-existing viral and bacterial infections, and have been taken off protective isolation. To date, this new form of gene therapy for X-SCID appears to be both safe and effective, if not fully curative, although more time will be necessary to fully evaluate this treatment. We believe this new approach provides the best way to treat X-SCID children that lack a matched sibling donor for stem cell transplant.

Scientific Abstract:
Early trials of gene therapy for X-linked Severe Combined Immunodeficiency (XSCID) restored T cell immunity in most cases, but did not correct B cell function and carried a high risk of iatrogenic leukemia. The subsequent development of self-inactivating \( \gamma \)-retroviral vectors has enhanced safety, but has not restored B cell function to date. We developed a new approach for XSCID gene therapy that utilizes a safety modified lentiviral (LV) vector (CL20-i4-EF1\( \alpha \)-hGC-OPT) together with reduced exposure busulfan (Bu) conditioning for newly diagnosed infants with XSCID. Recently, we reported that the combination of reduced dose Bu used together with our LV vector restored T and B cell function in older XSCID children with declining immune function following haploidentical transplantation (De Ravin SS et al, Sci Transl Med, 2016). Here we report initial results of LVXSCID-ND; a multi-center, phase I/II safety and efficacy study using our LV vector and dose-adjusted Bu for the first time in newly treated XSCID infants. We enrolled six subjects over the last 12 months (median age of 4.5 months, range: 2-12 months). Purified bone marrow (BM) CD34\(^+\) cells were transduced with the CL20-i4-EF1\( \alpha \)-hGC-OPT vector generated by a stable producer cell line and then cryopreserved to facilitate central manufacturing for multiple study sites and evaluation of release criteria prior to conditioning. Busulfan was given as two single daily doses to target a total cumulative area-under-the-curve (cAUC) of 22 mg\( \cdot \)hr/L (60-90 mg\( \cdot \)hr/L - myeloablative cAUC). The median dose of transduced CD34\(^+\) cells was 8.06 x 10\(^6\) cells/kg (range: 4.6 - 11 x 10\(^6\)) and the median vector copy number (VCN) in graft CFU-C was 0.40 copies /cell (range: 0.16 - 0.97). An average Bu cAUC of 22.9 mg\( \cdot \)hr/L (range: 20.0 to 24.2) was achieved, which was within 10% of the intended cAUC in all patients. As of July 2017, no severe adverse events related to BM harvest, Bu exposure, or cell infusion have been observed. In the
first 5 evaluable cases, complete hematopoietic recovery occurred by 3-4 weeks without any blood product support. Follow-up data from the oldest patient who presented with high levels of maternal T cell engraftment, severe neutropenia requiring G-CSF therapy, CMV viral infection, with a graft VCN of 0.16, and who is now 12 months post therapy, demonstrated delayed and partial T cell reconstitution. Cases 2 and 3 have been followed for nine and six months, respectively and have significantly higher VCNs in peripheral blood (PB) subsets (CD14/15+myeloid cells 0.65, 0.30 copies/cell; CD3+ T cells 2.78, 2.71; CD19+ B cells 1.01, 0.78; and CD56+ NK cells 2.72, 2.11 respectively). Bone marrow aspirates on week 16 yielded VCNs in sorted CD34+ cells of 0.56, 0.50, and BM myeloid CFU-GM of 0.61, 0.24. Rapid T cell reconstitution in cases 2 and 3 resulted in normal numbers of CD3+, CD4+, CD4 naïve, and CD5+ cells with TREC 626 and 1170 copies per ug DNA 16-20 weeks post therapy. In both cases at 16 weeks, T cell proliferation was 86% and 81% of control, and V-β spectratype scores were normal at 194 and 155. At nine months, case 2 had a normal isohemagglutinin anti-A titer of 1:32 and normal 4-week trough serum immunoglobulins levels (IgG 713 mg/dl, IgM 54 mg/dL and IgA 16 mg/dl). IVIG supplementation has been discontinued for approximately 3 months before vaccination responses are assessed. Case 4 has been followed for 12 weeks with PB VCNs for CD3+ cells of 1.36 copies/cell, CD19+ 0.58, CD56+ 1.38 and CD14/15+ 0.02. Flow cytometry analysis of PB at 12 weeks shows 4.5% of PB leukocytes are CD3+, with 61% CD4+, 11% CD8+, and a significant fraction expressing a CD45RA+, RO- naive phenotype at this early time point. Cases 5 and 6 are still too early to evaluate for immune phenotype and function. Preliminary vector insertion site analysis shows highly polyclonal marking patterns in case 2 with 11,000 insertion sites in CD3+ cells, 5,049 sites in CD19+ cells, 756 sites in BM myeloid CFU-C without any evidence of clonal dominance. In summary, gene therapy for newly diagnosed XSCID patients using a LV vector with targeted reduced exposure Bu conditioning is well tolerated and results in rapid T cell reconstitution in most cases. Efficient vector marking in bone marrow CD34+ cells, myeloid cells, and B cells indicate that this approach will likely provide broad immune reconstitution rather than restricted T cell correction seen in past trials using γ-retroviral vectors with no Bu.