Safety and Clinical Benefit of Lentiviral Hematopoietic Stem Cell Gene Therapy for Wiskott-Aldrich Syndrome

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Wiskott-Aldrich Syndrome (WAS) is an X-linked primary immunodeficiency characterized by thrombocytopenia, recurrent infections, eczema, autoimmunity and increased susceptibility to malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a recognized curative treatment for WAS, but is still associated with transplant-related complications and long-term morbidity, particularly in the absence of fully matched donors. In April 2010, we initiated a phase I/II clinical trial with hematopoietic stem cell (HSC) gene therapy (GT) for WAS. The investigational medicinal product (IMP) consists of autologous CD34+ HSC engineered with a lentiviral vector (LV) driving the expression of WAS cDNA from an endogenous 1.6 kb human WAS promoter (LV-WAS), infused after a reduced intensity conditioning (RIC) based on anti-CD20 mAb, targeted busulfan and fludarabine. We previously reported early follow up (FU) results from the first 3 patients (Aiuti et al., Science 2013). Seven patients (Zhu score ≥3) have now been treated at a median age of 1.9 years (1.1 – 11.1). As of May 2015, all patients are alive with a median FU of 3.2 years (0.7 – 5.0). CD34+ cell source was bone marrow (BM) (n=5), mobilized peripheral blood (MPB) (n=1) or both (n=1). IMP dose ranged between 7.0 and 14.1 $x10^6$ CD34+/kg, containing on average 94.4 ± 3.5% transduced clonogenic progenitors and a mean vector copy number (VCN)/genome in bulk CD34+ cells of 2.7 ± 0.8. No adverse reactions were observed after IMP infusion and RIC was well tolerated. Median duration of severe neutropenia was 19 days; granulocyte-colony stimulating factor was administered to 1 patient.

In the first 6 treated patients with FU >2 years, we observed robust and persistent engraftment of gene corrected cells. At the most recent FU, transduced BM progenitors ranged between 20.7 and 59.7%, and LV-transduced cells were detected in multiple lineages, including PB granulocytes (VCN 0.34 - 0.93) and lymphocytes (VCN 1.18 - 2.73). WAS protein expression, measured by flow-cytometry, was detected in the majority of PB platelets [mean ± standard deviation (SD), 71.4 ± 14.0%], monocytes (63.3 ± 18.5%) and lymphocytes (78.9 ± 14.9%). Lymphocyte subset counts were normal in most patients and proliferative response to anti-CD3 mAb was in the normal range in all 6 patients.

After immune reconstitution, a marked reduction in the annualized estimated rate of severe infections was observed, as compared with baseline (figure 1A). The first 6 treated patients discontinued anti-infective prophylaxis and no longer require a protected environment. Four patients stopped immunoglobulin supplementation and 2 of them developed specific antibodies after vaccination. Eczema resolved in 4 patients and remains mild in 2. No clinical manifestations of autoimmunity were observed ≥1 year after GT in accordance with improved B-cell development and decreased autoantibody production. All patients became platelet transfusion independent at a median of 4 months after GT (range: 1.0 – 8.7). Mean platelet counts progressively increased after treatment (mean ± SD: before GT, 13.4 ± 7.8 $x10^9$/l; 24-30 month FU, 45.8 ± 22.0 $x10^9$/l; 36-42 month FU, 57.0 ± 18.7 $x10^9$/l).

The frequency and the severity of bleeding events decreased after the 1st year of FU. No severe bleedings were recorded after treatment (figure 1B).

Quality of life improved in all patients after GT. From the 2nd year of FU, the number of hospitalizations for infections decreased and no hospitalizations due to bleeding were observed after treatment.
The seventh patient treated, who received MPB derived CD34+ cells only, showed the fastest platelet recovery with the highest level of transduced myeloid cell engraftment, and is clinically well.
No Serious Adverse Events (SAE) related to the IMP were observed. The most frequent SAE were related to infections (85%), occuring mainly during the 1st year of FU.
Importantly, no evidence of abnormal clonal proliferations emerged after GT and the LV integration profile show a polyclonal pattern, with no skewing for proto-oncogenes.
In conclusion, this updated report in 7 WAS patients show that GT is well tolerated and leads to a sustained clinical benefit. The high level of gene transfer obtained with LV-WAS results in robust engraftment of transduced HSC, even when combined with RIC. Prolonged FU will provide additional information on the long-term safety and clinical efficacy of this treatment.

Figure 1