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RETROVIRAL GENE THERAPY FOR THE TREATMENT OF ADA-SCID: LONG-TERM FOLLOW UP AND FIRST CASE OF T-CELL ACUTE LEUKAEMIA DUE TO INSERTIONAL MUTAGENESIS

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Background:

Haematopoietic stem cell (HSC) gene therapy (GT) using a γ-retroviral vector (γ-RV) (Strimvelis®) has been authorised in the EU for the treatment of Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID) in patients with no suitable human leukocyte antigen (HLA)-matched related HSC donor.

Aims:

We summarise our experience with ADA-SCID γ-RV GT during clinical development and post-marketing and report the occurrence of the first case of T-cell acute lymphoblastic leukaemia (T-ALL) after GT.

Methods:

Since 2000, 40 patients have been infused with autologous CD34+ cells engineered with a γ-RV encoding ADA following low dose busulfan. Patients were monitored long-term with annual visits. Eighteen patients were treated within the Clinical Development Program, 4 in a Named Patient Program (NPP), and 16 with the commercial product. Two patients were treated under Hospital Exemption with mobilised CD34+ peripheral blood cells, instead of bone marrow derived used for Strimvelis. Efficacy was evaluated in the first 36 patients with a sufficient follow-up (FU) up to March 5, 2020; serious adverse events were reported on the entire cohort until November 30, 2020.

Results:

All evaluable patients are alive with a median FU of 7.2 years (range 0.3-19.2) with an intervention-free survival of 83.3% (30/36). Of the 6 patients in whom GT failed, 4 underwent allogeneic HSCT and 2 were on long-term enzyme replacement therapy. In all 30 patients with successful outcomes, engraftment of gene corrected cells persisted long-term in multiple haematopoietic lineages, at higher levels in lymphocytes. ADA activity in mononuclear cells was sustained in most patients with adequate systemic detoxification. Immune reconstitution was accompanied in most patients by increased immunoglobulin production, decreased Ig use and antibody response to vaccines. Long-term FU data revealed a decreased rate of severe infections after treatment. Most adverse events were related to disease background, conditioning or immune reconstitution. A drug-related event recently emerged in an NPP patient of 5.75 years of age, who developed T-ALL 4.7 years after GT. Routine FU 3 months earlier did not reveal abnormalities and a polyclonal insertion site profile was present at 1, 1.5 and 3 years post-GT. Clinical onset consisted of haemorrhagic diathesis and weakness. Blood tests showed WBC 291.300/uL and immature lymphocytes (93%) with phenotype CD7+, CD34het, CD2+, CD56-, CD4-, CD8dim, sCD3dim/neg, cyCD3+. There was no CNS or mediastinal involvement. The blast population was transduced (1.18 VCN/genome) and expressed low ADA activity. Integration site analysis identified a single highly dominant clone harboring a vector integration ~40kb upstream the LMO2 gene, which was overexpressed by RT-PCR. Retrospectively, the insertion was found in mature peripheral blood CD4+ T cells at 1 year (7%), stable over time. Whole genome analyses in blasts revealed loss of a large part of chr. 6 and two large LOH regions on chr. 9. The patient showed poor prednisone response, while morphological complete remission was obtained at the end of induction therapy of the AIEOP-BFM ALL 2017 protocol. Further studies are ongoing to better characterize the factors contributing to leukaemogenesis in this patient.

Summary/Conclusion:

Efficacy of γ-RV-GT in ADA-SCID is sustained with a FU up to 19.2 years. Due to the identified risk of leukaemogenesis, patients will continue long-term FU to closely monitor the safety of the product. EMA CHMP confirmed that the risk/benefit balance remains favorable for Strimvelis in its approved indication.

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