Lentiviral vector-based gene therapy demonstrates long-term safety and efficacy for Wiskott-Aldrich Syndrome

February 10 2022

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Genethon, a unique non-profit gene therapy R&D organization founded by the French Muscular Dystrophy Association (AFM-Telethon), announced today that its lentiviral based gene therapy, developed in collaboration with French and British teams, has demonstrated long-term efficacy in eight patients with Wiskott-Aldrich syndrome, a rare and severe immune deficiency.

"These results confirm the stability and good tolerance of the lentiviral vector as a tool for gene transfer into blood stem cells," said Anne Galy, Ph.D., Inserm Research Director at Genethon. "Our teams have carried this project from translational research to a clinical trial by working with the best clinical and research teams internationally. We are delighted with the results of this trial which now show the long-term efficacy and safety of this approach for this rare and severe immune deficiency."

Frederic Revah, Ph.D., CEO of Genethon, added, "I would like to congratulate Anne Galy and her team who have been working on this project for more than 15 years in the service of patients and their families. This trial for Wiskott-Aldrich syndrome was the first international trial launched by our laboratory, and today 12 clinical trials are being conducted worldwide for products stemming from our R&D. From basic research to clinical development, Genethon has developed a unique expertise in the field of gene therapy for different families of rare diseases."

The long-term results of the WAS clinical trial, sponsored by Genethon and conducted by colleagues in France and England, were published in *Nature Medicine*, in a paper titled "Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott–Aldrich syndrome." The vector used in the study was designed, developed and manufactured by Genethon.

WAS, a rare and severe complex immune deficiency, is caused by a mutation in the WAS gene in hematopoietic progenitor cells, which are blood-forming cells. The inherited disease affects only boys and results in hemorrhages, repeated severe infections, severe eczema, and in some patients, autoimmune reactions and development of cancers. The only treatment currently available is bone marrow transplantation, which requires a compatible donor and can cause serious complications. Symptoms of the disease emerge at 6 months old and life expectancy for

severe forms is 3.5 years without treatment.

Genethon's gene therapy involves extracting from patients the blood stem cells carrying the genetic abnormality, correcting them in the laboratory with a healthy WAS gene and transplanting the cells back into the patients. Initial results from the clinical trial, published in the *Journal of the American Medical Association* in 2015 showed safety and efficacy along with stabilized engraftment of the blood cells 9 months to 42 months after the treatment.

Results from the longer term follow-up of eight patients for a median of 7.6 years confirm the stability of the transplanted genetically modified cells and their safety and efficacy. The gene therapy corrected major disease symptoms, improved or eliminated bleeding and signs of autoimmunity, and restored T-cell (or immune system) function. In addition, a 30-year-old patient was treated in the trial, demonstrating efficacy in adult patients whose thymus gland, which makes T-cells, was thought to be low- to non-functioning after many years of illness. Platelet levels remain low but gene therapy alleviates the need for platelet transfusions and prevents the occurrence of spontaneous hemorrhages.

More information: A. Magnani et al, Long-term safety and efficacy of lentiviral hematopoietic stem/progenitor cell gene therapy for Wiskott–Aldrich syndrome, *Nature Medicine* (2022). DOI: 10.1038/s41591-021-01641-x

Provided by AFM-Téléthon

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