

Institute of Child Health, Great Ormond Street Hospital NHS Trust, London, UK

Severe Adverse Event in Clinical Trial of Gene Therapy for X-SCID

We regret to inform you that one child out of 10 children treated has developed a T cell leukaemia following gene therapy for X-linked SCID at Great Ormond Street Hospital/Institute of Child Health in London.

This patient is now 3yrs old and was diagnosed in Sept 2005. Following careful counselling, his parents opted to enter the gene therapy protocol and he was treated in Dec 2005. He was the 8th child on the protocol to be treated. His clinical course until very recently has been extremely good with excellent T cell recovery. One month prior to the development of the leukaemia he was assessed and found to have a normal T cell subset analysis and no clinical evidence of lymphoproliferation. He subsequently went on to develop lethargy and bruising and hepatosplenomegaly at which point haematological investigations led to identification of the leukaemia. He is now under the care of the haematology/oncology team at Great Ormond Street Hospital and has started a standard T-ALL protocol. He is currently responding well to treatment, although these are very early days. Our best wishes are with the family and child.

Molecular analysis of the leukaemia is underway and only preliminary results are at present available. In collaboration with colleagues in Germany, we have established that the proto-oncogene LMO2 is overexpressed and that there is a nearby integration site. This gene has been dysregulated in a number of the severe adverse events in the Paris trial of X-SCID gene therapy and the mechanism of leukaemogenesis is therefore likely to be similar. Further analysis is ongoing and will be published in due course.

The vector used in the trial is an MFG based gammaretroviral vector with a GALV pseudotype and encoding the γ c gene. Culture conditions have previously been published (Gaspar et al., Lancet. 2004 Dec 18-31;364(9452):2181-7).

All other patients are currently well and are being informed of the event. All patients are monitored regularly and have not shown any evidence of abnormal clonal proliferations. This trial is now closed and the last child was treated in May 2006. We are working on an improved vector for gene therapy for X-SCID which has a decreased potential for leukaemogenesis and it is hoped that clinical trials with this new vector will start in 2008.

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