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Gene Therapy Starts to Tackle CNS Disease

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X-linked adrenoleukodystrophy (X-ALD) is a CNS demyelinating disorder caused by loss-of-function mutations in the *ABCD1* gene, which encodes the peroxisomal adenosine triphosphate-binding cassette transporter ALD. The ALD transporter imports very-long-chain fatty-acids into peroxisomes where they are degraded. X-ALD manifests often in boys between 5-12 years by progressive cerebral demyelination that results in a devastating neurologic degradation, and often death before adolescence. Adrenomyeloneuropathy (AMN) affects X-ALD adults males and heterozygous women and is characterized by a pure progressive myelopathy. However about 35% of AMN males develop also cerebral demyelination with the same poor prognosis as in boys. Allogeneic hematopoietic stem cell transplantation (HCT) has been shown to arrest cerebral demyelination in X-ALD boys and adults, provided the procedure is performed at an early stage of the disease. The long term beneficial effects of HCT in X-ALD are likely due to the progressive turn-over of brain microglia that are derived from myeloid progenitors in the bone-marrow. Finding a tissue-matched stem cell donor remains difficult, even with availablity of cord blood, and allogeneic HCT carries a high mortality risk (15-20% in children, and up to 40% in adults). To circumvent these problems, a new strategy was devised in which X-ALD patients were treated with their own genetically modified hematopoietic stem cells (HSCs). To allow *ex vivo* genetic correction of these HSCs prior to infusion, a self-inactivating lentiviral vector derived from HIV1 was used because it has the unique property to allow penetration of DNA material into the nucleus of cells that not divide or very little, like HSCs. CD34＋ cells were isolated from the peripheral blood of two patients with cerebral X-ALD who were candidate to allogeneic HCT but had no HLA-matched donor, and were transduced with a lentiviral vector containing the wild-type *ABCD1* gene. The patients underwent myeloablation to remove resident hematopoietic stem cells, and then received infusions of their own genetically modified cells. Up to 36 months after gene therapy, both patients showed expression of ALD transporter in a substantial proportion of their peripheral myeloid and lymphoid cells, indicating that the genetically corrected cells had engrafted successfully and that HSCs were transduced in the patients. Hematopoiesis remained polyclonal without evidence of clonal skewing or dominance due to insertion of lentiviral vector in or close to oncogenes. By 14-16 months after gene therapy, brain MRI scans revealed that cerebral demyelination had been arrested in both cases, without further changes up to the last follow-up of 36 months. Overall HSC gene therapy with lentiviral vector showed comparable clinical benefits to those observed after uncomplicated allogeneic HCT. These data have implications for X-ALD boys and adults who develop cerebral demyelination but also for all CNS diseases that can possibly be treated by allogeneic HCT. Other brain gene therapy strategies based on the intracerebral injection of promising gene therapy vector will also be discussed.

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