

Stem-Cell Gene Therapy for the Wiskott-Aldrich Syndrome

Boztug K, Schmidt M, Schwarzer A, et al. *N Engl J Med.* 2010;363(20):1918–1927

PURPOSE OF THE STUDY. To examine the efficacy of transfusion of autologous genetically modified hematopoietic stem cells for Wiskott-Aldrich syndrome (WAS). WAS is an X-linked recessive primary immunodeficiency disorder associated with thrombocytopenia, eczema, and autoimmunity.

STUDY POPULATION. Two 3-year-old boys with WAS were included. Inclusion criteria included severe WAS, no evidence of malignancy, and isolation of sufficient numbers of CD34⁺ cells.

METHODS. Autologous CD34⁺ cells were collected by leukopheresis. The cells were then transduced with WAS protein (WASP)-expressing retroviral vectors. The subjects were infused with busulfan. The cells were reinfused back into the subjects 4 days after they were transduced.

RESULTS. WASP expression was demonstrated in a variety of subgroups of leukocytes. At the level of hematopoietic stem cells in the bone marrow, stable chimerism of cells expressing WASP was demonstrated in both subjects. An increase in platelet counts was found starting 6 to 9 months after gene therapy. Improvement was also demonstrated in the function of a variety of subgroups of leukocytes, including natural killer cells, monocytes, T lymphocytes, and B lymphocytes. The frequency and severity of infection decreased in both patients. Signs and symptoms of autoimmunity and eczema disappeared. Comprehensive insertion-site analysis showed vector integration that targeted multiple genes controlling growth and immunologic responses in a persistently polyclonal hematopoiesis. These subjects had been followed for 3 years at the time of the report, and no clonal imbalance (indicating possible neoplastic growth) has been detected.

CONCLUSIONS. This study found that gene therapy for WAS is feasible and effective and, during the time of observation, is not associated with treatment-limiting adverse events.

REVIEWER COMMENTS. Add WAS to the list of disorders, including severe combined immunodeficiency, chronic granulomatous disease, and adrenoleukodystrophy, that have been treated with gene therapy. These results are fascinating and exciting.

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Nanofiltered C1 Inhibitor Concentrate for Treatment of Hereditary Angioedema

Zuraw BL, Busse PJ, White M, et al. *N Engl J Med.* 2010;363(6):513–522

PURPOSE OF THE STUDY. To determine the efficacy of nanofiltered C1 inhibitor concentrate in the management of hereditary angioedema (HAE).

STUDY POPULATION. Subjects were from 2 studies; the lowest age was 6 years (median age: 36 years).

METHODS. Both studies compared an intravenous dose of 1000 U of nanofiltered C1 inhibitor concentrate in the management of HAE. The first study end point was the time to unequivocal relief of symptoms during an acute attack of HAE. The second study was a crossover trial that involved 22 subjects; prophylactic twice-weekly infusions of drug (1000 U or placebo) was given during two 12-week periods. The primary end point in the second study was the number of attacks in the 12-week treatment period compared with placebo.

RESULTS. In the first study, the mean time of the onset of unequivocal relief of an attack was 2 hours in treated subjects compared with 4 hours in those given placebo ($P = .02$). In the second study, the number of attacks per 12-week period was 6.2 with active drug compared with 12.73 with placebo ($P < .001$). The treated subjects also had significant reduction in both the severity and duration of the attacks.

CONCLUSIONS. When given as treatment, the nanofiltered C1 inhibitor concentrate shortened the duration of acute attacks. When used for prophylaxis, the treatment reduced the frequency of acute attacks.

REVIEWER COMMENTS. This treatment allows for at least a 50% reduction in the frequency and duration of HAE attacks. In patients with less-severe clinical presentation for whom continuous treatment is not necessary, 2 preparations that are available for as-needed use are reported in the same issue of the journal (Cicardi M, Levy RJ, McNeil DL, et al. *N Engl J Med.* 2010;363[6]:523–531; and Cicardi M, Banerji A, Bracho F, et al. *N Engl J Med.* 2010;363[6]:532–541). Both are subcutaneous preparations given within 8 hours of attack onset. Both preparations showed significant efficacy with a <5-hour onset for relief of acute symptoms. An accompanying editorial provided important perspective regarding the efficacy of these treatments (Morgan BP. *N Engl J Med.* 2010;363[6]:581–583). These 2 studies allowed for therapy of HAE specific for the burden of the illness for each individual patient in a rare but potentially lethal disease.

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