tations before diagnosis, with respiratory and gastrointestinal symptoms being the most common. Infection rates improved with γ-globulin replacement therapy. Bronchiectasis secondary to respiratory infections was present in 7 of 22 patients and was the presenting finding for 5 of 7 patients. Allergy was diagnosed in 11 of 22 patients, but only 3 patients had positive specific allergen prick test results. CVID was diagnosed in 3 girls after they were found to have an autoimmune disease, which delayed the diagnosis for 1 patient who subsequently developed severe lung disease. Four patients had other family members with CVID or other primary immunodeficiency. Immunoglobulin G (IgG) levels (range: 80–552 mg/dL; median: 332 mg/dL) at the time of diagnosis did not correlate with the severity of clinical manifestations in children. Although results were not statistically significant, patients without MB cells (MB0 group) had more-severe complications, including bronchiectasis, persistent positive culture results, or autoimmune manifestations, compared with MB2 and MB1 groups.

CONCLUSIONS. Early diagnosis and treatment are important for patients with CVID. IgG levels at diagnosis did not correlate with the severity of clinical manifestations in pediatric patients with CVID; however, there was a trend suggesting that lack of MB cells might correlate with clinical severity and outcomes.

REVIEWERS COMMENTS. Contrary to findings among adult patients with CVID, IgG levels did not correlate with disease severity among children with CVID. Bronchiectasis was diagnosed in one third of pediatric patients with CVID and presented as early as 2.5 years of age. Providers should consider CVID in the differential diagnosis for young children with recurrent infections. The authors were able to demonstrate that MB cell classification correlates with the severity of clinical manifestations and may be an important marker to aid in the determination of prognoses for patients with CVID in the future.

**Gene Therapy for Immunodeficiency Due to Adenosine Deaminase Deficiency**


**PURPOSE OF THE STUDY.** To investigate the long-term outcome of gene therapy for severe combined immunodeficiency (SCID) attributable to the lack of adenosine deaminase (ADA), a fatal disorder of purine metabolism and immunodeficiency.

**STUDY POPULATION.** The study evaluated 10 children with SCID attributable to ADA deficiency who lacked a HLA-identical sibling donor. These patients had early manifestations of the deficiency (median age: 2 months) and underwent gene therapy at a median age of 1.7 years (range: 0.6–5.6 years).

**METHODS.** After nonmyeloablative conditioning with busulfan, the subjects received infusions of autologous CD34+ bone marrow cells that had been transduced with a retroviral vector containing the ADA gene. Enzyme-replacement therapy polyethylene glycol-modified bovine ADA (PEG-ADA) was not given after infusion of the cells.

**RESULTS.** All patients were alive after a median follow-up period of 4.0 years. Transduced hematopoietic stem cells had stably engrafted and differentiated into myeloid cells containing ADA and lymphoid cells. Eight patients did not require enzyme-replacement therapy, their blood cells continued to express ADA, and they had no signs of defective detoxification of purine metabolites. Nine patients had immune reconstitution with increases in T-cell counts and normalization of T-cell function. In the 5 patients for whom intravenous immunoglobulin replacement was discontinued, antigen-specific antibody responses were elicited. Serious adverse events included prolonged neutropenia (2 patients), hypertension (1 patient), central venous catheter-related infections (2 patients), Epstein-Barr virus reactivation (1 patient), and autoimmune hepatitis (1 patient).

**CONCLUSIONS.** Gene therapy, combined with reduced-intensity conditioning, is a safe, effective treatment for SCID in patients with ADA deficiency.

**REVIEWER COMMENTS.** This group previously reported gene therapy for ADA deficiency in 2 patients, and this article includes the long-term outcomes of those patients as well as 8 others. Because the mortality rates for patients with ADA deficiency who receive transplants from unrelated or haploidentical donors are quite high, this report represents a significant advance. Because, with gene therapy for ADA deficiency, there is less selective pressure for the survival of stem cells that may have vector integrations that may lead to activation of oncogenes, it is less likely that these patients will experience the T-cell lymphoproliferative syndrome that affected some of the patients in the previously reported trials of gene therapy for X-linked SCID. It is hoped that the principles learned in these trials of gene therapy for children affected with SCID will be used in the further development of gene therapy for these and other genetic diseases.
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