Mutations in TNFRSF13B Encoding TACI Are Associated With Common Variable Immunodeficiency in Humans

PURPOSE OF THE STUDIES. To search for mutations of TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor; also TNFRSF13B) in patients with common variable immunodeficiency (CVID) and immunoglobulin A deficiency (IGAD).

STUDY POPULATIONS. Salzer et al screened 162 unrelated individuals with CVID. Castigli et al studied 19 unrelated individuals with CVID and 16 with IGAD. Healthy individuals (100 and 50, respectively) served as controls.

METHODS. Genomic DNA from patients was subjected to reverse transcription and polymerase chain reaction sequencing analysis of the 5 exons of the gene encoding TACI. Binding of mutant TACI to ligands and stimulation of immunoglobulin production in vitro with TACI agonists in patients was also studied.

RESULTS. Salzer et al identified 13 individuals with CVID who had mutations in TACI. Castigli et al identified 4 individuals with CVID and 1 with IGAD and TACI mutations. None of the 150 controls studied had any of the identified TACI mutations. Interestingly, TACI mutations could cause disease in both the heterozygous and homozygous conditions. Patients’ cells had diminished binding to TACI ligands and showed diminished responses (immunoglobulin production) to TACI agonists in vitro. The clinical characteristics of the patients included hypogammaglobulinemia and impaired antibody responses, recurrent bacterial sinopulmonary infections, autoimmune disease (anemia, thyroiditis, positive antinuclear antibody), lymphoproliferative disease, and malignancy (B-cell lymphoma, gastric carcinoma).

CONCLUSIONS. Approximately 8% to 20% of patients with severe combined immunodeficiency or IGAD may have heterozygous or homozygous mutation in TACI. This genetic alteration should be sought in patients with these disorders.

REVIEWER COMMENTS. CVID and IGAD are among the most prevalent humoral immunodeficiencies at all ages. These studies represent important descriptions of defined mutations in patients with CVID and IGAD occurring in a significant fraction of these patients in 2 relatively genetically disparate populations. The ability to clearly define the underlying cause of disease in these patients will immediately lead to greater accuracy and confidence in diagnosis, earlier and more aggressive therapy, and, hopefully, improved outcomes.

Gene Therapy of X-Linked Severe Combined Immunodeficiency by Use of a Pseudotyped Gammaretroviral Vector

PURPOSE OF THE STUDY. To investigate the application of somatic gene therapy for X-linked severe combined immu-
nodeficiency (SCID-X1) in patients without an HLA-matched donor for bone marrow transplant.

STUDY POPULATION. All 4 children with SCID-X1 resulting from a γ-c chain mutation and without an HLA-identical sibling referred to Great Ormond Street Hospital (London, United Kingdom) between July 2001 and December 2002 were offered and consented to receive gene therapy.

METHODS. The complete coding region of human γ-c was cloned into a pMFG gammaretroviral vector and transfected into bone marrow CD34+ stem cells for reinfusion into the patients. T-cell function was assessed by responses to mitogens, Candida antigen, and mixed lymphocyte reactions. T-cell receptor (TCR) repertoires were assessed by direct immunofluorescence with fluorescein-conjugated antibodies to TCRV-β. Additional longitudinal studies including enhancer-mediated activation of the T-cell protooncogene LMO-2. Additional longitudinal studies will help to determine the duration of reconstitution and quantify the risk of adverse events.

RESULTS. At reinfusion, 27% to 58% of cells were CD34-positive and γ-c-positive. In all patients, natural killer cells appeared 2 to 4 weeks postinfusion and remained at low-normal levels. Naive CD45RO-, CD27+ T cells appeared at 10 to 30 weeks. Two patients developed normal numbers of CD3, CD4, and CD8 cells, allowing discontinuation of prophylactic medications. One of these patients developed a maculopapular rash on the palms and soles after CD4 T-cell recovery. Another patient had gastrointestinal bleeding resulting from rejection of engrafted maternal cells. The eldest patient, who received gene therapy at 33 months of age, had slower lymphocyte recovery. All patients developed normal T-cell–proliferative responses to mitogens, antigens, and mixed lymphocyte reactions. One year after treatment, all patients showed acute neutrophilic folliculitis with perivascular inflammation with a predominance of eosinophils. A skin biopsy revealed patchy interstitial and intra-alveolar inflammation with eosinophils. Bone marrow biopsy demonstrated a hypercellular marrow with predominantly eosinophils, which is consistent with idiopathic HES.

CONCLUSION. After somatic gene therapy, all 4 patients with SCID-X1 had significant improvement in clinical and immunologic function without serious adverse events.

REVIEWER COMMENTS. Morbidity and mortality are high in patients with SCID-X1 for whom an HLA-matched family donor is not available. This small study suggests that substantial, prolonged immunologic recovery is possible with somatic gene therapy; however, recovery of thymopoiesis may be compromised in older patients. Previous studies have shown more serious adverse events, including enhancer-mediated activation of the T-cell protooncogene LMO-2. Additional longitudinal studies will help to determine the duration of reconstitution and quantify the risk of adverse events.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2006-0900888

Elinor Simons, MD
Albany, NY

Pediatric Hypereosinophilic Syndrome (HES) Differs From Adult HES

PURPOSE OF THE STUDY. To highlight specific differences between pediatric and adult patients with hypereosinophilic syndrome (HES).

STUDY POPULATION. The case report involved a 15-year-old male who presented with abdominal pain, diarrhea, and a 10-lb weight loss. Colonoscopy revealed colitis. A nonproductive cough, night sweats, and a diffuse pruritic, papular rash developed. His initial absolute eosinophil count was 1890/mm³ (reference: <400/mm³), which increased to 52 000/mm³. Additional laboratory studies included: immunoglobulin E, 8561 U/mL (7–110 U/mL); alkaline phosphatase, 1149 U/mL (reference: 50–280 U/mL); γ-glutamyl transpeptidase, 193 (reference: 0–50 U/mL); and serum tryptase, 4.7 µg/L (reference: 1.9–13.5 µg/L). Ultrasound of the liver revealed an abnormal parenchymal pattern with dilated bile ducts. Molar analysis of the patient’s peripheral blood for the Fip1-like-1 platelet-derived growth factor receptor α chain (FIP1L1-PDGFRA) fusion tyrosine kinase associated with HES in adults was negative. Open lung biopsy revealed patchy interstitial and intra-alveolar inflammation with a predominance of eosinophils. A skin biopsy showed acute neutrophilic folliculitis with perivascular dermatitis with eosinophils. Bone marrow biopsy demonstrated a hypercellular marrow with predominantly eosinophils, which is consistent with idiopathic HES.

METHODS. The investigators compared this case report of pediatric HES and additional published cases of pediatric and adult patients with HES.

RESULTS. Pediatric HES has only a slight male predominance (55.3% male vs 44.7% female), whereas adult HES is reported to be more common among males than females, with a ratio of 9 to 1. In adults, the frequencies of symptoms found on presentation are: fatigue (26%), cough (24%), dyspnea (16%), rash (12%), and fever (12%). Fever (58.8%), arthralgias (23%), and rash (23.5%) were more common in pediatric cases. As with adults, involvement of the cardiovascular system is the major source of morbidity and mortality. Pediatric HES is commonly associated with chromosomal abnormalities,