overexpression of TSLP in the lungs or skin also promoted peripheral basophilia. This systemic basophilia resulted from TSLP-triggered expansion of bone marrow precursor cells through a mechanism independent of IL-3 signaling. Basophils were present in TSLP-deficient mice, indicating that TSLP was not essential for normal basophil development. In comparison with classical basophils induced by IL-3, TSLP-elicited basophils expressed higher levels of TH2-skewing cytokines and proinflammatory mediators. Furthermore, basophils obtained from patients with eosinophilic esophagitis, a disease associated with mediator production, and addicts with aberrant TSLP production, were phenotypically distinct from those found in healthy controls.

CONCLUSIONS. Abnormal TSLP production at 1 barrier surface may promote development of allergic inflammation at other sites by increasing the number and altering the function of circulating basophils.

REVIEWER COMMENTS. It is well known that patients with 1 allergic disorder are likely to develop others, but the mechanisms for this “atopic march” remain obscure. Here, the authors show an important role for the cytokine TSLP, which has been shown to be highly expressed in animal and human tissues with active allergen-driven inflammation. The ability of TSLP to expand and alter the phenotype of peripheral basophils may promote the development of allergic disease at other barrier surfaces and could explain why patients with atopic dermatitis frequently go on to develop asthma or food allergy. In addition to contributing to our understanding of the biology of allergic diseases, these studies also identify TSLP as a potentially important target for pharmacological blockade in vulnerable patients.


The Wisconsin Approach to Newborn Screening for Severe Combined Immunodeficiency


PURPOSE OF THE STUDY. Severe combined immunodeficiency (SCID) is a life-threatening disease of infants that is curable with hematopoietic cell transplantation if detected early, whereas the outcome is less favorable if treatment is delayed. The study evaluated outcomes of a screening program in Wisconsin.

STUDY POPULATION. Newborns in Wisconsin over a 3-year period.

METHODS. Population-based screening for SCID by using the T-cell receptor excision circle (TREC) assay applied to samples obtained from routine newborn screening (Guthrie) cards has been underway in the state of Wisconsin since 2008.

RESULTS. Five infants with SCID or other forms of severe T-cell lymphopenia (TCL) have been detected out of a total...
of 207,696 infants screened between January 1, 2008, and December 31, 2010. Based on these data, the specificity of this screening assay is 99.98% with a false-positive rate of 0.018%. In addition, the positive predictive value of this test as applied for identifying a severe TCL due to any cause was 45.83%. Among 9 infants without other secondary causes for the TCL, 5 had reversible TCL, and 4 had 22q11.2 microdeletion (DiGeorge) syndrome. Importantly, it appears that no infants with SCID have been missed during this screening period.

CONCLUSIONS. TREC assay screening as part of routine newborn screening detects infants with severe TCL in a cost-effective fashion and should be adopted as a part of routine newborn screening as currently recommended by the US Department of Health and Human Services.

REVIEWER COMMENTS. This report provides the cumulative experience of newborn screening by using the TREC assay over a 3-year period in Wisconsin, proving that it is an effective means of identifying newborns with severe TCL associated with immune deficiencies including SCID and complete DiGeorge syndrome. Importantly, this experience also proved that the TREC assay is unreliable in premature infants such that their current practice is to repeat the TREC assay until an infant reaches an adjusted gestational age of 37 weeks at which time it is viewed as reliable. One clear conclusion from these data is that an infant with severe TCL identified by an abnormal TREC assay should undergo a complete immunologic evaluation managed by an experienced clinical immunologist. Another unanticipated finding from this experience is the fact that there are rare newborns with TCL but normal T-cell function, and as more of these infants are identified it will become clearer as to how they should best be managed. It should be noted that the results of an abnormal TREC assay are available early enough to prevent immunizations with live viral vaccines and exposure to unirradiated blood products until the immune status of the infant is clarified, a situation that should prevent unnecessary complications from these agents.

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Excellent Survival After Sibling or Unrelated Donor Stem Cell Transplantation for Chronic Granulomatous Disease


PURPOSE OF THE STUDY. To determine outcomes and survival in patients with chronic granulomatous disease (CGD) after hematopoietic stem cell transplantation (HSCT) in both HLA-matched related (MRD) and unrelated donor (MUD) transplants.

STUDY POPULATION. This is a single-center retrospective cohort study of 11 children with a diagnosis of CGD, a history of at least 1 invasive infection, and 70% meeting parameters indicative of high-risk disease. Nine children had X-linked CGD, 1 had autosomal recessive CGD, and 1 did not have an identifiable mutation. Nine of the 11 patients were boys, and mean age at transplantation was 3.8 years (range: 11 months to 13 years).

METHODS. Of the 11 patients studied, 4 received HSCT from 6/6 HLA-MRDs (siblings); 7 received HSCT from 10/10 HLA-genoidentical MUDs. All patients underwent busulfan-based myeloablation (with addition of cyclophosphamide, cytarabine, or fludarabine) and graft-versus-host disease (GVHD) prophylaxis with cyclosporine A. Time to engraftment was defined as time from transplantation to time of neutrophil count >500 cells/μL for 3 consecutive days. B- and T-cell recovery was measured by flow cytometry, and lymphoproliferative responses were measured by response to mitogens and antigens. Chimerism was measured in each patient.

RESULTS. Nine patients achieved full donor chimerism, whereas 2 had stable mixed chimerism. A neutrophil count of >500 cells/μL was reached at a median of 18 days for the cohort. Time to engraftment was not significantly different between MRD and MUD recipients, as measured by recovery of neutrophils, platelets, CD3+ and CD4+ T cells, and T-cell proliferative responses. Oxidative burst was normal by day 100 in all patients. Grade 1 acute GvHD of the skin occurred in 4 of 11 patients, 3 of whom received MUD transplants. One patient had a relapse of Aspergillus-associated pneumonia initially acquired before engraftment. Patients were followed for a mean of 4 years (range: 1–8 years), and all are well with significant improvements in quality of life, including the ability to attend school with no special care requirements.

CONCLUSIONS. The study reveals 100% survival at mean follow-up time of 4 years, no severe or chronic GvHD, no graft failure, and only 1 incidence of recurrent infection before engraftment for MRD and MUD transplant recipients. The authors suggest that both MRD and MUD HSCT should be considered early in the course of CGD in children with severe invasive infection.

REVIEWER COMMENTS. Where previously HSCT was recommended only in patients with HLA-MRDs, these results suggest that earlier HSCT with related or unrelated donor stem cells provides good outcomes and low complication rates, and this may lead to improved survival and quality of life in patients with CGD as well as less end-organ damage.

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