A prospective study on the natural history of patients with profound combined immunodeficiency: An interim analysis

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Background: Absent T-cell immunity resulting in life-threatening infections provides a clear rationale for hematopoetic stem cell transplantation (HSCT) in patients with severe combined immunodeficiency (SCID). Combined immunodeficiencies (CIDs) and "atypical" SCID show reduced, not absent T-cell immunity. If associated

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with infections or autoimmunity, they represent profound combined immunodeficiency (P-CID), for which outcome data are insufficient for unambiguous early transplant decisions.
Objectives: We sought to compare natural histories of severity-matched patients with/without subsequent transplantation and to determine whether immunologic and/or clinical parameters may be predictive for outcome.
Methods: In this prospective and retrospective observational study, we recruited nontransplanted patients with P-CID aged 1 to 16 years to compare natural histories of severity-matched patients with/without subsequent transplantation and to determine whether immunologic and/or clinical parameters may be predictive for outcome.
Results: A total of 51 patients were recruited (median age, 9.6 years). Thirteen of 51 had a genetic diagnosis of "atypical" SCID and 14 of 51 of CID. About half of the patients had less than 10% naive T cells, reduced/absent T-cell proliferation, and at least 1 significant clinical event/year, demonstrating their profound immunodeficiency. Nineteen patients (37%) underwent transplantation within 1 year of enrolment, and 5 of 51 patients died. Analysis of the HSCT decisions revealed the anticipated heterogeneity, favoring an ongoing prospective matched-pair analysis of patients with similar disease severity with or without transplantation. Importantly, so far neither the genetic diagnosis nor basic measurements of T-cell immunity were good predictors of disease evolution.
Conclusions: The P-CID study for the first time characterizes a group of patients with nontypical SCID T-cell deficiencies from a therapeutic perspective. Because genetic and basic T-cell parameters provide limited guidance, prospective data from this study will be a helpful resource for guiding the difficult HSCT decisions in patients with P-CID. (J Allergy Clin Immunol 2017;139:1302-10.)

Key words: *T-cell deficiency, combined immunodeficiency, hematopoietic stem cell transplantation, natural history*

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Human genetic disorders leading to deficiencies in T-cell number and/or function are a heterogeneous group of inherited diseases. They can range from absent T-cell immunity with early onset of severe clinical manifestations to significant residual T-cell immunity with late onset of milder clinical manifestations. The characteristic clinical feature of complete T-cell deficiencies is infection susceptibility, while incomplete T-cell deficiencies in addition present with manifestations of impaired immune regulation and malignancy.[1-4] The key treatment to restore T-cell immunocompetence is hematopoetic stem cell transplantation (HSCT) and in some cases gene therapy or enzyme replacement therapy. There is little debate that this intensive therapy is required to prevent lethal complications in patients with absent T-cell immunity. However, the threshold of T-cell immunity required to prevent severe clinical complications is unknown. In patients with low to intermediate T-cell function, it is therefore frequently difficult to make a prognosis and to balance this prognosis against the risks of HSCT.

Currently, there is no accepted classification of T-cell deficiencies established from this therapeutic perspective (for present classifications of T-cell disorders, see Table E1 in this article's Online Repository at www.jacionline.org). Patients with very low T-cell numbers are usually classified as severe combined immunodeficiency (SCID). Although these patients have a clear HSCT indication, this classification does not consider that there are also patients with normal T-cell numbers, but severely impaired T-cell function with the same risk for early severe complications and the same clear HSCT indication (eg, ORAI calcium release-activated calcium modulator 1 [ORAI1], caspase recruitment domain family, member 11, or IkBkB deficiency or patients with the IL-2 receptor gamma chain [IL2RG]^{R222C} mutation). At the other end of the spectrum, common variable immunodeficiency (CVID), although predominantly an antibody deficiency,[5] can be associated with significantly impaired T-cell immunity and manifestations related to this.[6,7] Current definitions also do not consider a threshold of T-cell immunity below which the diagnosis of CVID is inappropriate and early HSCT is a necessary consideration. Preliminary criteria for a threshold of T-cell immunity separating CVID from more profound T-cell deficiencies, which we derived by expert consensus in the European Society for Immunodeficiencies (ESID) Registry Working Group, remain to be prospectively validated.[8]

In this study, we focus on patients with disorders of T-cell immunity that can neither be classified as SCID nor as CVID, but rather as combined immunodeficiencies (CIDs). Our present article considers the following categories of CID, including "atypical SCID," taking into consideration the previous work of Roifman et al[3] and Felgentreff et al[14]: (1) "bona fide" CID, diseases in which mutations in affected genes cause T-cell deficiencies and the clinical problem is mainly restricted to the immune system (eg, lymphocyte-specific protein tyrosine kinase, IL2-inducible T-cell kinase [*ITK*], zeta-chain (TCR)-associated protein kinase 70kDa [*ZAP70*], macrophage stimulating 1, Coronin 1A, dedicator of cytokinesis 8, dedicator of cytokinesis 2, and MHC class I and II deficiencies).[9-13] A subgroup are syndromic CID, diseases in which mutations cause additional clinical problems (eg, cartilage hair hypoplasia, severe cases of 22q11 deletion syndrome, Cernunnos, and *STIM1* or purine nucleoside phosphorylase deficiencies); (2) atypical SCID,[14] in which patients survive infancy despite T-cell deficiencies caused by hypomorphic mutations in SCID-associated genes (eg, recombination-activating genes [*RAG*] 1/2, DNA cross-link repair 1C [*DCLRE1CI*], *IL2RG*, *ORAI1*, or inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta [*IKBKB*]); and (3) CID of unknown cause, in which T-cell deficiency can be documented, but no disease-causing mutation is detected. We label patients from 1 of these 3 groups of patients with CID as

Abbreviations used
CID: Combined immunodeficiency
CVID: Common variable immunodeficiency
HSCT: Hematopoietic stem cell transplantation
IL2Rg: IL-2 receptor gamma chain
ITK: IL2-inducible T-cell kinase
NBS: Newborn screening
ORAI1: ORAI calcium release-activated calcium modulator 1
P-CID: Profound combined immunodeficiency
QOL: Quality of life
RAG: Recombination-activating gene
SCID: Severe combined immunodeficiency
ZAP70: Zeta-chain (TCR)-associated protein kinase 70kDa