

Letter to the Editor

Survey on retransplantation criteria for patients with severe combined immunodeficiency

To the Editor:

Although hematopoietic stem cell transplantation (HSCT) has been an accepted life-saving therapy for severe combined immunodeficiency (SCID) for more than 40 years, with progressive improvement in 10-year survival rates,^{1,2} there is a lack of consensus as to best approaches. In particular, in these young and vulnerable patients, there is a well-founded desire to use no or minimal conditioning before transplantation. In spite of their immunodeficiency, however, patients with SCID may manifest graft rejection or loss. The definition(s) of graft failure and the indication(s) for delivery of a “boost” (defined as additional graft from the same donor without conditioning)² or retransplantation (defined as additional graft from either the same or a different donor with conditioning) have been the subject of keen debate among transplant physicians caring for these patients.

At workshops of the Primary Immune Deficiency Treatment Consortium, which represents 33 centers in North America,³ it became evident that different centers have individual approaches to retransplantation for patients with SCID, particularly with respect to indication, and when and how to retransplant. With the aim of better defining these criteria, we conducted a survey among 20 North American and 5 European transplant centers to elicit feedback about their policy and experience on these issues. In this survey, we considered 2 clinical situations in which retransplantation may be considered: (1) graft failure and (2) persistent immune dysfunction despite stable engraftment. Because the approach to HSCT differs from center to center, we sought to determine the criteria used to define graft failure on the basis of 6 proposed situations: no conditioning regimen (CR), reduced-intensity conditioning (RIC) regimen, and full myeloablative conditioning (MAC) regimen, for each of which transplantation with

or without T-cell depletion (TCD) was considered. The survey was meant to capture the policy at each center for patients with typical SCID.⁴

The questionnaire (designed by E.H., M.C., and L.N. and sent to each center) was completed by the principal investigator (PI) of each center. To define graft failure, each PI was asked to respond to close-ended questions based on the conditioning regimen in use at that center. Center PIs were given the choice of various criteria for defining the absence of T-cell engraftment and the absence of myeloid engraftment. For persistent immune dysfunction despite stable engraftment, the survey included both open- and close-ended questions and did not take into consideration the CR/TCD regimen used (see this article's [Online Repository E1](#) at www.jacionline.org). The center PIs who reported that patients with SCID with persistent immune dysfunction despite T-cell engraftment were not considered for retransplantation at their center were asked to not respond to further questions.

Most centers selected “undetectable CD3⁺ T cells” or “absence of donor T-cell chimerism” to define the absence of donor T-cell engraftment, and “ANC [absolute neutrophil count] < 500/uL” or “ANC > 500 but no donor myeloid cells detected” to define the absence of myeloid engraftment. As expected, in the absence of a CR, most centers considered lack of T-cell engraftment as the only criterion needed to define graft failure post-HSCT ([Table I](#)). Surprisingly, approximately one third of the center PIs included the absence of myeloid engraftment as an additional criterion for graft failure even though without myeloablation, myeloid engraftment is unlikely. After a full MAC or RIC regimen, most centers (~60%) required lack of both T-cell and myeloid engraftment as criteria for defining graft failure. In contrast, depending on the CR (MAC or RIC) and the presence or absence of TCD, 10% to 20% and 21% to 40% of the centers considered that lack of T-cell engraftment alone or myeloid engraftment alone, respectively, was sufficient to define graft failure ([Table I](#)).

TABLE I. Definition of graft failure after HSCT for patients with SCID

HSCT regimen	Myeloid and T-cell criteria						T-cell criteria time frame post-HSCT	Myeloid criteria time frame post-HSCT
	T-cell criteria only	Myeloid criteria only	T-cell and myeloid criteria at the same time	Myeloid criteria followed by T-cell criteria	T-cell criteria followed by myeloid criteria			
Centers performing transplantation without conditioning (no CR)								
No CR (N = 24)*	16 (66%)	—	8 (33%)	—	—	2 mo (median, 2 mo)	—	
No CR + TCD (N = 15)*	11 (73%)	—	4 (27%)	—	—	3.63 mo (median, 3 mo)	—	
Centers performing transplantation with RIC								
RIC (N = 21)*	6 (29%)	2 (9.5%)	2 (9.5%)	9 (43%)	2 (9%)	2.36 mo (median, 2 mo)	1.93 mo (median, 2 mo)	
RIC + TCD (N = 10)*	4 (40%)	—	2 (20%)	4 (40%)	—	3.4 mo (median, 3 mo)	1.83 mo (median, 2 mo)	
Centers performing transplantation with full MAC								
MAC (N = 19)*	4 (21%)	3 (16%)	5 (26%)	7 (37%)	—	2.25 mo (median, 2 mo)	1.6 mo (median, 2 mo)	
MAC + TCD (N = 14)*	4 (29%)	2 (14%)	1 (7%)	7 (50%)	—	3.25 mo (median, 3 mo)	1.4 mo (median, 1 mo)	

*N is the number of centers performing the regimen and responding to the question. This explains that while a total of 25 centers participated in the survey, the denominator for total N in many categories is fewer than 25.

TABLE II. Criteria for retransplantation after stable engraftment but persistent immune dysfunction

Criteria	No. of centers selecting the response (N = 23 total)*
Laboratory evidence of T-cell dysfunction	21
Defined as:	
CD3 ⁺ T-cell count <500/mm ³	15
T-cell proliferation to mitogen <20% of lower limit of controls	12
T-cell proliferation to antigens <10% of lower limit of controls	10
Oligoclonal T-cell repertoire	9
Other:	7
CD3 ⁺ T-cell count <200/mm ³	1
Poor TREC equivalent or absence of naive T-cell count	2
CD4 ⁺ T-cell count <100/mm ³	1
Low T cells with infections	1
Infections in general	1
"Whole clinical picture"	1
B-cell dysfunction (absent antibody production)	2
Autoimmunity	10
GvHD	3
Infections (new or failure to clear infection)	16
Absence of myeloid engraftment	4
Other clinical or laboratory criteria:	
Chronic pulmonary disease	1
CD45RA ⁺ T cell, TRECs	1
Growth failure	1

GvHD, Graft versus host disease; TREC, T-cell receptor excision circle.

*N = 23: Only 23 centers (among 25 participating) confirmed that patients with SCID with T-cell chimerism, but persistent immune dysfunction could be considered for retransplantation and only these centers continued the survey.

The interval needed to define lack of T-cell engraftment posttransplant was 2.00 to 2.36 months (median, 2 months) for HSCT without TCD and 3.00 to 3.63 months (median, 3 months) for HSCT with TCD, independent of the regimen. In contrast, absence of myeloid engraftment post-HSCT was defined between 1 and 2 months (median) for MAC or RIC, independent of using TCD in either regimen. Importantly, despite the general trends illustrated (Table I), the exact criteria used to define graft failure varied widely among the individual centers. For instance, some centers defined graft failure at 1 month as the absence of myeloid engraftment, whereas other centers defined it as the absence of T-cell engraftment at 6 months after HSCT.

Because some patients may have persistent immune dysfunction despite stable engraftment,⁵⁻⁷ we evaluated the criteria used at each center to define poor immune reconstitution and if, when, and how patients with SCID with persistent immune dysfunction should be retransplanted. Overall, 23 of the 25 centers confirmed that patients with SCID with donor T-cell chimerism but persistent immune dysfunction would be considered for retransplantation. Center PIs identified biological evidence of T-cell dysfunction (21 of 23), recurrent/severe infections (16 of 23), and autoimmunity (10 of 23) as the main criteria for considering retransplantation (Table II). There was a reasonable agreement among centers on the definition of T-cell dysfunction (Table II).

Interestingly, even though 21 of 23 center PIs selected T-cell dysfunction as the main criterion for retransplantation, only 12 of 23 responded that isolated T-cell dysfunction without clinical

signs would be sufficient to consider retransplantation and 11 of 23 PIs reported that second transplants would require that T-cell dysfunction be associated with clinical signs of recurrent infections and/or autoimmunity. Twenty-one of the 23 PIs responded that they would use the same donor (if available) for retransplantation, and in such case, 12 of 21 would consider using a CR. In contrast, 5 center PIs reported they would not use a CR and 4 responded that the decision to use a CR would depend on additional criteria, such as chimerism, presence of infection, and/or type of donor. Almost all center PIs (20 of 23) considered that retransplantation with a different second donor should be performed with a CR. There was lack of consensus regarding the time frame for performing retransplantation, because 9 of 23 center PIs reported that it was not a question of time, while among the other 14 centers, the majority answered within 1 year (n = 8) and fewer centers (n = 3) indicated within a time frame of 2 years post-HCT. Finally, in response to an open-ended question, most centers indicated that decisions regarding retransplantation in this context are very difficult and that it is hard to define criteria.

This survey shows that despite some trends, there is a lack of consensus on criteria to define graft failure or indications for retransplantation of patients with typical SCID who attain poor immune reconstitution. To date, few studies^{1,5,7} have investigated the details of long-term clinical and immunologic function for patients with SCID post-HCT. The quality of the immune reconstitution may vary depending on the molecular defect of the patient; for instance, T-cell reconstitution is better in B⁺ SCID than in B⁻ SCID⁵ and functional B-cell reconstitution is better if there is donor B-cell engraftment in case of X-linked and JAK-3 SCID.^{8,9} However, only formal prospective and retrospective studies, such as those ongoing from the Primary Immune Deficiency Treatment Consortium,^{3,4,10} will be able to demonstrate the impact of specific molecular defects on immune reconstitution, better delineate the clinical and laboratory markers of poor immune reconstitution, and compare the impact of retransplantation or not on the overall survival of patients with poor immune reconstitution.

The following centers contributed to the survey: North American centers: CHU Sainte-Justine, Montreal, Quebec, Canada; Children's Hospital Boston, Boston, Mass; UCSF Benioff Children's Hospital, University of California, San Francisco, Calif; Baylor College of Medicine, Houston, Tex; Children's Hospital Los Angeles, Los Angeles, Calif; The Children's Hospital of Philadelphia, Philadelphia, Pa; Children's Memorial Hospital, Chicago, Ill; Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; Duke University, Durham, NC; Memorial Sloan-Kettering Cancer Center, New York, NY; Cardinal Glennon Children's Medical Center, St Louis, Mo; University of Utah, Salt Lake City, Utah; University of Michigan, Ann Arbor, Mich; University of Alabama at Birmingham, Birmingham, Ala; University of Texas Southwestern Medical Center, Dallas, Tex; Children's National Medical Center, Washington, DC; Doernbecher Children's Hospital, Portland, Ore; Methodist Children's Hospital of South Texas, San Antonio, Tex; Stanford University, Stanford, Calif; and Children's Healthcare of Atlanta, Atlanta, Ga. European centers: Hôpital Necker-Enfants Malades, Paris, France; Universitäts-Kinderklinik, Ulm, Germany; The Queen Silvia Children's Hospital, Gothenburg, Sweden; Great Ormond Street Hospital, London, United Kingdom; and Newcastle General Hospital, Newcastle, United Kingdom.

Elie Haddad, MD, PhD^{a,b}

Zoufia Allakhverdi, PhD^b

Linda M. Griffith, MD, PhD^c

Morton J. Cowan, MD^d

Luigi D. Notarangelo, MD^{e,f}

From ^athe Division of Pediatric Immunology, Allergy and Rheumatology, Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada; ^bCHU Sainte-Justine Research Centre, Montreal, Quebec, Canada; ^cthe Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md; ^dthe Division of Pediatric Allergy, Immunology, and Blood and Marrow Transplant, Benioff Children's Hospital, University of California San Francisco, San Francisco, Calif; ^ethe Division of Immunology and the Manton Center for Orphan Disease Research, Children's Hospital Boston, Boston, Mass; and ^fthe Harvard Stem Cell Institute, Harvard Medical School, Boston, Mass. E-mail: elie.haddad@umontreal.ca.

The Primary Immune Deficiency Treatment Consortium is supported by the Division of Allergy, Immunology and Transplantation, National Institute of Allergy and Infectious Diseases; the Intramural Research Programs of the National Human Genome Research Institute and the National Institute of Allergy and Infectious Diseases; and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, Md: U54-AI082973 (PI: M. J. Cowan), U54-NS064808 (PI: J. P. Krischer), and R13-AI094943 (PIs: M. J. Cowan and L. D. Notarangelo).

The opinions expressed are those of the authors and do not represent the position of the National Institute of Allergy and Infectious Diseases, the National Human Genome Research Institute, the Office of Rare Diseases Research, the National Center for Advancing Translational Sciences, the National Institutes of Health, or the US government.

This article was presented at the Primary Immune Deficiency Treatment Consortium First Annual Scientific Workshop, April 7-9, 2011, San Francisco, Calif, supported in part by the Immune Deficiency Foundation, Towson, Md; the Jeffrey Modell Foundation, New York, NY; the Robert A. Good Immunology Society, St Petersburg, Fla; Baxter International, Deerfield, Ill; CSL Behring, King of Prussia, Pa; and Talecris Biotherapeutics, Research Triangle Park, NC.

Disclosure of potential conflict of interest: E. Haddad has received travel support from the Primary Immunodeficiency Treatment Consortium. L. M. Griffith is employed by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH). M. J. Cowan has received research support from the NIAID and the NIH. L. D. Notarangelo has received research support from the NIH and March of Dimes; is a board member for the Program in Cellular and Molecular Medicine, the University Pediatric Hospital in Florence, the *Journal of Allergy and Clinical Immunology*, the *Journal of Clinical Immunology*, and *Clinical Immunology*; is employed by Boston Children's Hospital; and receives royalties from UpToDate. Z. Allakhverdi declares no relevant conflicts of interest.

REFERENCES

1. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol* 2010;126:602-10, e1-11.
2. Teigland CL, Parrott RE, Buckley RH. Long-term outcome of non-ablative booster BMT in patients with SCID. *Bone Marrow Transplant* 2013;48:1050-5.
3. Griffith LM, Cowan MJ, Notarangelo LD, Kohn DB, Puck JM, Pai SY, et al. Primary Immune Deficiency Treatment Consortium (PIDTC) report. *J Allergy Clin Immunol* 2013 Oct 15 [Epub ahead of print]. 10.1016/j.jaci.2013.07.052.
4. Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan B, et al. Diagnosing SCID, leaky SCID and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. *J Allergy Clin Immunol* 2014 [in press].
5. Haddad E, Landais P, Friedrich W, Gerritsen B, Cavazzana-Calvo M, Morgan G, et al. Long-term immune reconstitution and outcome after HLA-nonidentical T-cell-depleted bone marrow transplantation for severe combined immunodeficiency: a European retrospective study of 116 patients. *Blood* 1998;91:3646-53.
6. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, et al. Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. *N Engl J Med* 1999;340:508-16.
7. Neven B, Leroy S, Decaluwe H, Le Deist F, Picard C, Moshous D, et al. Long-term outcome after hematopoietic stem cell transplantation of a single-center cohort of 90 patients with severe combined immunodeficiency. *Blood* 2009;113:4114-24.
8. Haddad E, Leroy S, Buckley RH. B-cell reconstitution for SCID: should a conditioning regimen be used in SCID treatment? *J Allergy Clin Immunol* 2013;131:994-1000.
9. Buckley RH, Win CM, Moser BK, Parrott RE, Sajaroff E, Sarzotti-Kelsoe M. Post-transplantation B cell function in different molecular types of SCID. *J Clin Immunol* 2013;33:96-110.
10. Dvorak CC, Cowan MJ, Logan BR, Notarangelo LD, Griffith LM, Puck JM, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the Primary Immune Deficiency Treatment Consortium Prospective Study 6901. *J Clin Immunol* 2013;33:1156-64.

<http://dx.doi.org/10.1016/j.jaci.2013.10.022>

Online Repository:

E1. Survey on Re-Transplantation for Classical SCID

Part 1: Graft failure.

1) The first question is: how and when do you define graft failure under following regimens:

- No Conditioning / no T cell depletion
- No Conditioning / T cell depletion
- Reduced-intensity Conditioning / no T cell depletion
- Reduced-intensity Conditioning / T cell depletion
- Full (Myeloablative) Conditioning / no T cell depletion
- Full (Myeloablative) Conditioning / T cell depletion

Note: Check all that apply (only under regimen you perform at your center)

	Timing to re-transplant (i.e. How long do you wait?)						
	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	> 6 mo
CD3 undetectable							
CD3 < 5%							
CD3 < ___% (please specify)							
Absolute CD3 < ____ (please specify)							
No donor T cells detected							
No donor mononuclear cells detected							
Absolute neutrophil count < 500							
ANC >500 but no donor myeloid cells							

detected							
Other:							

17 **Part 2: Persistent immune dysfunction despite stable engraftment**

18 1) Do you believe that some patients transplanted for SCID and who have donor cells detected
19 but persistent immune dysfunction should be considered for a re-transplantation?

20 Yes

21 No

22 If you answer No, don't answer to the other questions

23 2) By which time post-transplantation do you consider re-transplantation for these patients?

24 - 3 months

25 - 6 months

26 - 12 months

27 - 18 months

28 - 2 years

29 - >2 years Specify: _____yrs

30 - It doesn't depend on the time

31 3) What is (are) the criteria that you use for indication for re-transplantation (indicate all that
32 apply)

33 - T-cell dysfunction

34 - B-cell dysfunction

35 (absent antibody production)

36 - autoimmunity

37 - GvHD

38 - infections

39 (new or failure to clear infection)

40 one center : possibly, depends on type of infection

41 one center : if infection is inducing cytopenias

42 - absence of myeloid engraftment

43 - other clinical or laboratory criteria? if yes, please list

44 4) How would you define a T-cell dysfunction that would make you consider re-transplantation

45 (check all that apply)

46 - < 500 CD3⁺ /mm³

47 - < 1000 CD3⁺ /mm³

48 - T cell proliferation to mitogen:
49 < 20% of control
50 <30% of control
51 <50% of control
52
53 other specify <___%
54 - T cell proliferation to antigen low/absent
55 (i.e., < 10% of lower limit of controls)
56 -Oligoclonal T cell repertoire
57 - Other specify _____
58 5) Do you consider re-transplantation in a patient with only T-cell dysfunction (good clinical
59 status, no infection, no autoimmunity)
60 Yes
61 No
62 If not, which other criteria are necessary? _____
63 6) If same donor is available, would you use the same donor?
64 Yes
65 No
66 7) Would you use conditioning for re-transplantation with the same donor?
67 Yes
68 No
69 With second donor?
70 Yes
71 No