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Long term Outcome of Non-Ablative Booster Bone Marrow Transplantation in Patients with Severe Combined Immunodeficiency

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Abstract

Severe combined immunodeficiency (SCID) is a fatal syndrome caused by mutations in at least 13 different genes. It is characterized by the absence of T-cells. Immune reconstitution can be achieved through non-ablative related donor bone marrow transplantation. However, the first transplant may not provide sufficient immunity. In these cases, booster transplants may be helpful. A prospective/retrospective study was conducted of 49 SCID patients (28.7 percent of 171 SCIDs transplanted over 30 years) who had received booster transplants to define the long term outcome, factors contributing to a need for a booster and factors that predicted success. Of the 49 patients, 31 (63 percent) are alive for up to 28 years. Age at initial transplantation was found to have a significant effect on outcome (mean of 194 days old for patients currently alive, versus a mean of 273 days old for those now deceased, p=0.0401). Persistent viral infection was present in most deceased booster patients. In several patients, the use of two parents as sequential donors resulted in striking T and B cell immune reconstitution. A majority of the patients alive today have normal or adequate T-cell function and are healthy. Non-ablative booster bone marrow transplantation can be life-saving for SCID.

Keywords

Booster; bone marrow transplantation; severe combined immunodeficiency; 2-parent bone marrow transplants

Introduction

Severe combined immunodeficiency (SCID) is a fatal syndrome characterized by the absence of T cells and, in some molecular types, also of B or NK cells.[1,2] Without immune reconstitution by hematopoietic stem cell transplantation or gene therapy, infants with SCID will die in the first two years of life. The use of HLA identical or haploidentical allogeneic bone marrow stem cell transplantation without pre-transplant chemotherapy or post-

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Conflict of Interest

No author has either financial or intellectual conflicts of interests to disclose.

transplantation graft-versus-host disease (GVHD) prophylaxis has resulted in a survival rate at this institution of 94% if SCID patients are transplanted prior to 3.5 months of age.[2–4] However, the survival rate is significantly lower in those presenting later and, in some cases, patients fail to achieve immune reconstitution after one transplant. For such patients, "booster" transplants from the same or different donors have been given in efforts to achieve immune reconstitution.[5]

Most of what has been reported about booster bone marrow transplantation has been in cancer patients.[6–8] Booster transplantations have been reported to improve T-cell immunity in SCID patients[5] and in those with other primary immunodeficiencies[9,10] who had received a chemoablated first transplant. We report here the longterm outcomes in 49 SCID infants all of whom had initially received non-ablative T-cell-depleted haploidentical transplants and who subsequently received one or more non-ablative booster bone marrow transplants at this institution from 1982–2012 in efforts to improve their immune reconstitution.

Subjects and Methods

Patients

Forty-nine of 171 (28.7%) severe combined immunodeficiency (SCID) patients who received non-ablative T cell-depleted haploidentical parental bone marrow transplants at this institution from 1982–2012 received 1 to 3 subsequent transplants from either the same (N=29) or a different (N=20) donor for a total of 81 additional transplants. All 49 patients met criteria of the World Health Organization for the diagnosis of SCID, and none had "leaky" SCID or Omenn syndrome.[11] The age at diagnosis ranged from 0 days to 1.7 years. Comparisons of age at first transplant and survival in boosted and non-boosted patients are shown in Table 1 according to the molecular type of SCID. The different donors included the other parent (N=17), an HLA-identical sibling (N=2), a grandmother (N=1) or matched unrelated cord blood donors (N=5). Two patients received booster transplants only in an attempt to reconstitute B-cell function. Conditioning was used only in patients who received matched unrelated donor cord blood transplants (N=5). Additionally, one patient received a thymus transplant between her second and third stem-cell transplants. Three patients received gene therapy elsewhere following three, four, and two transplants at this institution, respectively; this was unsuccessful in all cases.[12] Only one of the 3 surviving boosted ADA-deficient patients is receiving PEG-ADA therapy, and all 3 of the deceased ones received it. Finally, four patients received additional matched unrelated donor transplants at other institutions following transplants at this institution and two subsequently died. Altogether, 18 boosted patients died. The control subjects for all immunological studies were healthy adult volunteers. The studies were approved by the Duke University Institutional Review Board, and written informed consent was obtained from the parents of all patients.

Immunologic Studies

Humoral and cellular immune studies were performed approximately every 3 weeks until T-cell function was established, then every three months for the next nine months, every six months for the following two years, then annually.

Serum Immunoglobulin and Antibody Measurements—Serum IgG, IgA, IgM and IgE were quantified by single radial diffusion or nephelometry.[13] Anti-diphtheria and anti-tetanus antibodies were determined by tanned cell hemagglutination[14] or by an ELISA after standard vaccines had been administered, and isohemagglutinins were measured by a microtiter plate assay.

Flow Cytometry and T-Cell Function—Lymphocyte phenotypes were determined by immunofluorescent staining of PBMC or whole blood with labeled antibodies to CD3, CD4, CD8, CD14, CD16, CD20, CD45RA, CD45RO, CD132, CD56, TCRαβ, and TCRγδ from BD Biosciences, San Jose, CA and multi-color flow cytometry. Lymphocyte proliferation was assessed by measuring [^{3}H] thymidine incorporation into PBMCs following culture with the stimuli.[15]

T-Cell Depletion—Donor bone marrow was rigorously depleted of T-cells by soybean lectin agglutination followed by two cycles of rosetting with sheep erythrocytes treated with aminoethylisothiuronium bromide, reducing the number of T-cells by a factor of 10,000.[3,16,17]

Chimerism—This was detected using karyotyping, fluorescence in situ hybridization or short tandem repeats.

Statistical Methods—Statistical comparisons were made using the Mann-Whitney U test for non-parametric analyses and Student's t-test or Chi-square for parametric data. All analyses were performed using Stata 12 (College Park, Tx).

Results

Of the 49 patients receiving booster transplants, 31 (63 %) are alive today, a survival rate lower than the 80.3% survival rate in the 122 non-boosted SCIDs (Table 1) and the 75% survival rate for the entire group. The length of survival ranges from 0.33 to 27.6 years from their first transplant (Supplementary Figure 1).

Factors associated with need for booster transplantation

Infections and poor or no immune reconstitution—The average time for donor T cells to appear in SCID infants after a successful rigorously T cell depleted stem cell transplant is from 90 to 120 days post-transplantation.[15] If a SCID patient had no or poor T cell function at between 120 and 180 days post-transplantation, particularly if there was a chronic viral infection, he or she was considered for booster transplantation. If there was no T cell function or chimerism, the other parent was used as the donor for the booster transplant. If there was some but inadequate T cell function despite donor T cell chimerism, the donor used for the first transplant was used for the booster.

Age at initial transplantation—This was significantly correlated with need for a booster transplant. Patients who required booster transplantation were an average of 223 days old at initial transplantation (SD 131), whereas patients who did not require booster transplantation

were an average of 165 days at initial transplantation (SD 152). This difference was significant (t=−2.3358, N=171, P=0.0207).

Factors influencing survival of the boosted patients

Age at Initial Transplantation—The effect of age at the time of the first transplantation on survival of the boosted patients is displayed in Supplementary Figure 2. The average age at initial transplantation for those who are currently alive was 194 days (S.D. 111) and for those who are deceased, the average age at initial transplantation was 273 days (S.D. 148). This difference was found to be significant (t=−2.1117, N=49, P=0.0401).

Sex, Race and Ethnicity—No significant differences in survival were found. Seventy-one percent of non-Hispanic white patients survive, whereas only 50 percent of the 8 Hispanic and 4 black patients survive (X^2=5.3566, N=49 P=0.253).

Type of Molecular Defect—The sample sizes were too small to evaluate statistically whether the molecular defect had an effect on mortality (Table 1).

Donor Source of Transplanted Cells—Of the 42 patients who received only haploidentical booster transplants, 27 (64%) are still alive. Of the 27 who received a booster only from the same parent, 17 (63%) survive, and of the 14 who received a booster from the other parent, 10 (71%) survive. Only 2 of 5 (40%) patients who received a matched unrelated cord blood transplant are alive, and the patient who received a booster transplant from his grandmother died. The 2 patients who received HLA-identical donor subsequent transplants both survive.

Number of Nucleated Marrow Cells Given—The number of nucleated bone marrow cells per kilogram given in the original transplant to the 49 booster transplantation patients was not significantly different from the number of cells given to all other SCID patients transplanted at this institution (z=1.647, N=171, P=0.0996) (Supplementary Table 1). However, the average number of cells per kilogram for the “booster” transplants was significantly lower (z=7.517, N=200, P<0.0001), as the patients were older and weighed more (z=−10408, N=200, P<0.0001).

Transplantation Interval—The mean interval between the first and second transplants in living patients was 1262 days (S.D. 1737, N=31) vs. 326 days for deceased patients (S.D. 323, N=18). The difference between means was significant (t=−2.2534, N=49, P=0.0289).

Graft-versus-Host Disease—Of all 171 SCID patients transplanted at this institution since 1982, 54 (32%) developed GVHD. Among the entire group, those who had GVHD were not more likely to require a booster transplant. Only 14 (28.6%) of the 49 boosted patients experienced GVHD following their first transplant and only one developed it after a booster transplant The latter patient developed fatal grade IV GVHD after a chemoablated matched unrelated cord blood transplant elsewhere. The boosted patients who had GVHD following their original transplant were no more likely to require more than one booster transplant than those who did not (X^2=4.8782, N=49 P=0.181).

Infections—Eleven of the 18 deceased patients died of one or more clinically apparent viral infections: three of cytomegalovirus, one of EBV lymphoproliferative disease, two of rotavirus, two of adenovirus, two of varicella, two of parainfluenza 3, and one of a herpes simplex infection. One patient died of a fungal infection, one of gram negative sepsis, one of an undefined neurologic disease, two of pulmonary complications, one of hemorrhage following surgery and one of graft-vs-host disease.

Other than viral infections, *Pneumocystis jiroveci* pneumonia and oral moniliasis were found to be most common at presentation and resolved with appropriate therapy. All but 4 deceased patients had a clinically documented chronic viral infection, whereas 93.33% of living patients have never had a clinically documented chronic viral infection. This difference was highly significant (X^2=24.85, N=47 P<0.0000).

Current Clinical Statuses—The 31 living patients' current clinical statuses were evaluated in 6 categories and a score was calculated with 6 being the most unhealthy. Patients were included in this evaluation if they had been seen within the last 2 years or had responded to a recent questionnaire (N=28).[18] The categories were regular antibiotic use, ADHD, neurological issues, gastrointestinal issues, receiving Cs or lower in school, and being in the 5th percentile or below in height or weight. The average clinical total score was 1.8 (S.D. 1.6).

Immune Reconstitution

Lymphocyte Enumeration and T-Cell Function—All infants lacked T-cells prior to initial transplantation. As expected, transplants that resulted in improved immune function were more often found in patients who are now alive. Shown in Table 2 are the latest results of immune evaluations in all patients. The absolute numbers of CD3 (z=3.609, p=0.0003) and CD4 (z=4.096, P<0.0001) positive T cells were significantly higher in the surviving patients, but the percentage of CD45RA positive T cells was not significantly different when compared to that of the deceased (z=1.535, p=0.1247). Improved T-cell function, measured by lymphocyte proliferation assays, was used to assess immune reconstitution. If a patient had one response greater than 50,000 CPM to any of the mitogens tested, the transplant was considered to have "improved T-cell function." Seventy-five of 130 transplants given to these patients resulted in improved T-cell function; 62 (78%) of these transplants were in patients who are currently living, while only 13 were in patients who are deceased. This difference was found to be highly significant (p<0.0000 X^2=32.4369, N=129). Mean responses to PHA (cpm) at the latest evaluations were also significantly higher in the living patients (z= 4.210, p<0.0001) (Table 2).

B-cell Function—B-cell function has proven difficult to reconstitute in SCID patients.[3,19–21] Two patients reported here (#'s 9 and 18, Table 2) were given boosters solely to gain B-cell function, and both failed. Currently, only 9 (29%) of the boosted patients have normal B cell function and do not require IG (Table 2). By contrast, 57 of the 98 (58%) non-boosted SCID patients who survive have B cell function and no longer require IG replacement.[21]

Patients with Two Parental Donors

In 7 of the 10 surviving patients who were given a booster transplant only with marrow from the other parent, T-cell function improved remarkably and became normal in 6 of these cases. One CD3 epsilon-deficient SCID patient received her first transplant from her father, but because she showed no immune function at 183 days post-transplantation, she was given a rigorously T-cell-depleted maternal marrow transplant (Figure 1). One month following the administration of the second transplant (maternal marrow), the patient's T-cell proliferation improved to 53,237 CPM to Con A. However, T-cell chimerism studies at the time demonstrated that the proliferating T-cells were 100% of paternal origin. She subsequently demonstrated T-cell chimerism from both parents, but the paternal T-cells dominated. Because her T-cell function was still not normal, a third transplant was given, this time again from her father, and she subsequently developed and maintained normal T-cell function and remains healthy at age 24. She also has normal B-cell function and does not require IVIG.

Figure 2 shows the post-transplantation course of a boy with IL7Rα-Def SCID who received his first haploidentical transplant from his mother. No immune reconstitution was evident at 174 days post-transplantation. A T-cell-depleted haploidentical transplant was then given from his father. His T-cell function subsequently developed normally and has been sustained. Chimerism studies have shown all of his T-cells to be of paternal origin. He has normal B-cell function and does not require IG. He is now healthy at age 23 years.

One boy with IL7Rα-Def SCID who received his first two transplants from his mother had no immune reconstitution at 408 days post-transplantation (Figure 3). A rigorously T-cell-depleted haploidentical transplant was then given from his father. He subsequently developed normal T-cell function and normal immunoglobulin levels. His T-cell chimerism is paternal. He is now 3.5 years old and healthy.

A Jak3-Def SCID also had a remarkable improvement in her T-cell function following a transplant from the other parent, as previously reported.[22] She had received two paternal transplants without achieving adequate T-cell function or engraftment. Finally, following a third transplant of maternal origin, normal T-cell function was achieved. Chimerism studies have shown that she has 2% paternal cells and 98% maternal T-cells. She also has normal B-cell function and does not require IVIG. She is now 8.5 years old and healthy.

Discussion

Our studies demonstrate that non-ablative booster transplantation is an effective means of enhancing immune system reconstitution following an unsatisfactory initial non-ablative T-cell-depleted HLA-haploidentical bone marrow transplant. The explanation for the higher rate of failure of haploidentical transplants (as opposed to HLA identical transplants) is unknown but appears to be related to the necessity to rigorously T cell deplete. In most cases, booster transplants were effective in improving immune function. No pre-transplant conditioning was used for any of the first or booster haploidentical transplants. Conditioning was used only prior to matched unrelated donor umbilical cord blood transplants. Omitting toxic chemoablative agents prior to bone marrow transplantation in SCID allows the patients

to avoid later infertility, veno-occlusive disease and damage to the lungs, endocrine organs, or brain.[23–25]

No increased incidence of GVHD following the first transplant was found when boosted patients were compared to non-boosted patients. In both groups, most of the donors were mismatched haploidentical parents whose marrow was rigorously T-cell depleted. Therefore, there was no need in either group for immunosuppressive drugs to be given for GVHD prophylaxis post-transplantation.

As with non-booster transplanted SCID patients, opportunistic viral infections and malnutrition were the main factors associated with mortality in booster-transplanted SCID patients.[3] Chronic viral infections were the most lethal complication among booster SCID patients, and in most patients these viral infections were present prior to their original transplant. All but four of 18 deceased patients in this study had clinically documented chronic viral infections and these were the direct cause of death in eleven. Early diagnosis and isolation are key to preventing infection in all SCIDS.[4,26]

The underlying molecular defect had little effect on the need for a booster transplant, with the exception of RAG1 and RAG2-deficiency, where 6 of 7 transplanted SCIDs required booster transplants. In the case of ADA-deficient SCID, often considered problematic for achieving engraftment,[27] this Center has transplanted 26 such patients over the past 30 years. Twenty (77%) survive and only 6 required booster transplants. Three of the six deceased had been given booster transplants. Two received successful gene therapy,[28] one received an ablated transplant elsewhere, and two are receiving PEG-ADA. The other fifteen are alive and well and are chimeric with related donor T cells after rigorously T cell-depleted non-ablative haploidentical parental (n=10, 2 boosted) or HLA identical (n=5) bone marrow transplants.

The use of bone marrow from both parental donors sequentially can improve immune reconstitution in some patients. In some cases, we found that the recipients became double parental chimeras, although usually chimerism with one parent's cells dominated. This is somewhat similar to the situation seen when multiple cord blood units are given to one recipient, in which case chimerism from one particular unit becomes dominant.[29] Although the factors that determine dominance of one donor over another have not been clarified, immune-mediated mechanisms are suspected. This was clearly the case in one such patient in our group who failed two paternal T-cell-depleted haploidentical bone marrow transplants but rapidly became immune reconstituted after her mother's T-cell-depleted haploidentical bone marrow transplant.[22] In that case, we suspected the later-identified transplacentally-transferred maternal T-cells rejected the paternal marrow transplants. Closer HLA matching of one haploidentical parent to the patient as opposed to the other parent's matching was examined, but review of the HLA typing data (not shown) found that in only one of the examples given was there such a possibility.

Booster transplantation has proven to be an effective means of prolonging life in SCID patients. Though the survival rate among booster patients (63%) is lower than the overall SCID survival rate at this institution (75%),[2] this is most likely due to the fact that the

patients who received boosters were older at the time of initial transplantation and were sicker, primarily with chronic viral infections. Without receiving a booster transplant, these patients would not have survived. Clinically, most surviving booster transplanted patients are doing well. The majority have adequate T-cell function. As in our previous studies of the entire group, age at transplantation was a key factor in survival,[4] most likely because the older patients were already infected with viral agents. Recognition of the beneficial effect of very young age on treatment outcome was an important factor in securing approval for newborn screening for SCID.[26] (3000 words)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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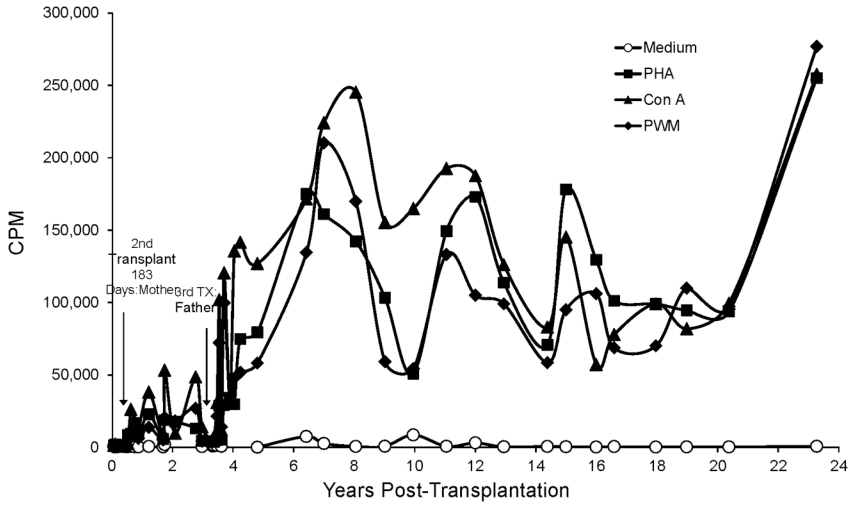

Figure 1.

The development of T cell function following sequential bone marrow transplants in a girl with CD3 epsilon deficient SCID. Her father was the first donor, but due to the lack of T cell function at 183 days post-transplantation, she received a rigorously T cell-depleted booster transplant from her mother. Following that, she developed some T cell function but chimerism studies revealed that most of the dividing cells were from her father. A third rigorously T cell-depleted transplant was then given from her father and she has subsequently gone on to have excellent long term T cell reconstitution. Subsequent T cell chimerism studies have revealed some chimerism from both parents, with the dominant chimerism being from the father. She does not require IVIG therapy although her B cells are all host.

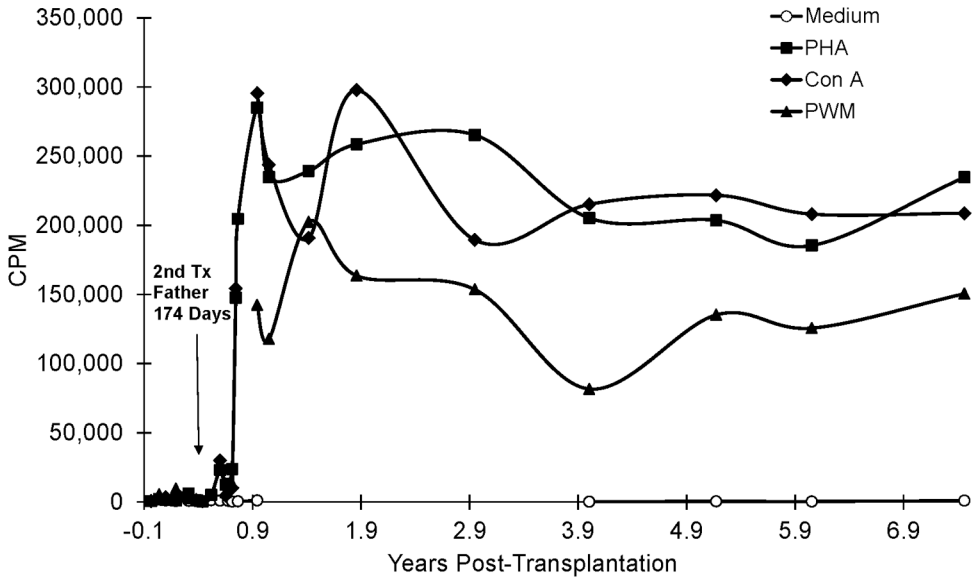

Figure 2.

Development of T cell function in an IL7Rα-Def SCID boy following two rigorously T cell-depleted haploidentical bone marrow transplants. The second one was given after T cell function had failed to develop at 174 days post-transplantation of marrow from his mother. The second transplant was marrow from his father, following which he developed and sustained excellent T cell function. Chimerism studies reveal the T cells to be all paternal. He does not require IVIG therapy although his B cells are all host.

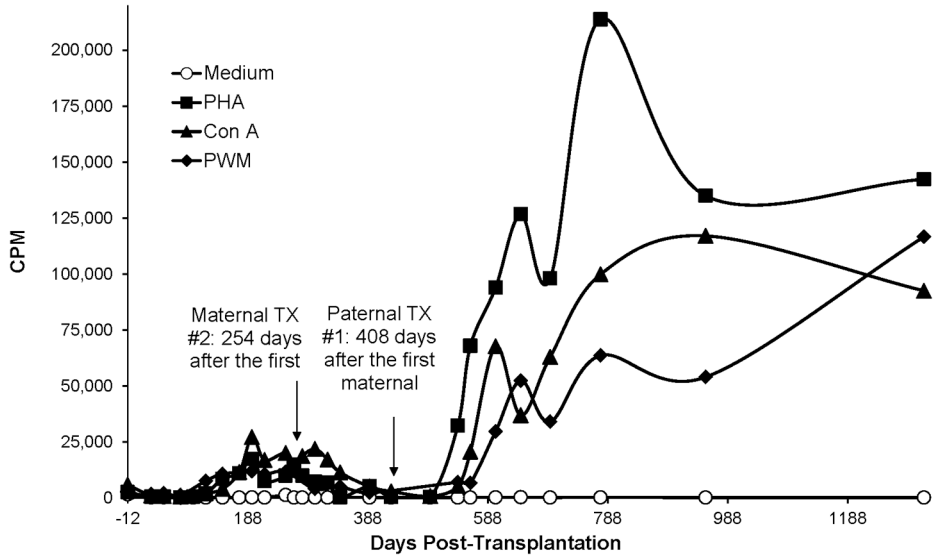

Figure 3.

Development of T cell function in another IL7Rα-Def SCID boy following three rigorously T cell depleted haploidentical parental bone marrow transplants. The mother was the donor for the first two, but T cell function failed to develop after either transplant, so a third transplant was given from the father and was subsequently followed by the development of sustained normal T cell function and paternal T cell chimerism.

Table 1

Comparisons of Age at Initial Transplant and Survival in Boosted and Non-Boosted SCIDs According to Molecular Type

Defect:	**ADA Def**	**Auto Rec**	**CHH**	**CD45 Def**	**CD3ε Def**	**Cd3ζ Def**	**Cd3δ Def**	**Artemis Def**	**RAG 2 Def**	**RAG 1Def**	**IL7Rα Def**	**Jak3 Def**	**X-linked**	**Unknown**	**Totals Mn ± SD**
# Boosted	6	6	1	0	1	1	0	0	5	1	7	4	15	2	**49**
Mean Age (Da) 1st BMT	179	241	207	NA	171	395	NA	NA	164	25	259	296	226	205	**223§ ± 130**
# Booster Transplants	7	10	1	0	2	3	0	0	10	2	11	7	24	4	**81**
# Dead Boosted	3	3	0	NA	0	1	NA	NA	1	0	3	1	4	2	**18***
# Non-Boosted	20	9	0	1	0	0	2	3	0	1	17	5	62	2	**122**
Mean Age (Da) 1st BMT	133	171	NA	341	NA	NA	124	473	NA	128	210	175	146	148	**165§ ± 152**
# Dead Non-Boosted	3	1	0		0	0	0	2	0	0	4	0	13	1	**24****

* 18/49= 63% Boosted survival rate.

** 24/122=80.3% Non-boosted survival rate.

§ p=0207

Table 2

Latest Immune Function in Boosted Patients

Pat. No.	SCID Type	Age (da) 1st Trans*	# Boosts	D→R Sex**	Days to 1st Boost	Days to Last Boost	Donor B cells	mg/dl IgA	mg/dl IgM	IG RX***	Donor T Cells	#/cmm CD3	#/cmm CD4	#/cmm CD8	% CD3+ CD45RA+	% CD3+ CD45RO+	TREC μg/ml	Medium CPM	PHA CPM	Yrs Post Trans*
	Alive																			
1	ADADef	112	1	F-F→M	2908	NA	Yes	78	44	0	Yes	514	297	152	ND	ND	N.D.	4,460	40,447	23.68
2	ADADef	182	2	F-F-M→M	145	702	No	67	63	1	No	107	61	36	7.0	67.0	112	191	24,257	15.22
3	ADADef	135	1	F-F→M	4074	NA	No	5	224	1	Yes	457	266	142	11.8	69.4	N.D.	1,738	24,846	12.59
4	AutoRec	147	2	F-M-F→M	168	154	No	0	0	1	ND	509	478	31	ND	ND	N.D.	149	24,056	14.40
5	AutoRec	170	2	F-F-M→F	1251	1374	No	0	0	1	ND	58	26	32	8.0	56.0	<100	108	7,296	12.52
6	AutoRec	303	1	F-M→F	215	NA	No	7	10	1	Yes	506	352	142	41.2	37.0	N.D.	190	137,615	3.29
7	CartHair	207	1	F-F→M	4515	NA	No	0	0	1	Yes	1925	834	1170	32.8	45.6	N.D.	194	2,443	22.45
8	CD3εDef	171	2	M-F-M→F	183	1027	No	108	121	0	Yes	551	440	94	13.8	57.9	1,130	691	255,038	23.56
9	RAG2Def	119	2	F-F-F→M	1381	2198	No	0	0	1	Yes	241	97	127	2.3	76.2	<100	166	23,457	24.10
10	RAG2Def	395	3	F-F-F-F→M	586	699	No	0	0	1	Yes	559	301	247	6.8	64.2	<100	86	16,058	11.65
11	RAG2Def	33	2	F-F-F→M	329	1430	No	12	0	1	Yes	27	26	1	1.6	91.6	N.D.	1,620	18,089	6.58
12	RAG2Def	162	1	F-F→M	616	NA	No	0	4	1	Yes	314	154	154	2.0	71.8	<100	203	62,602	6.10
13	RAG1Def	25	2	F-F-M→M	189	483	No	0	0	1	Yes	1197	378	582	9.8	77.9	<100	226	226,290	8.22
14	IL7RαDef	164	1	F-M→M	174	NA	No	259	113	0	Yes	903	509	426	53.1	23.6	906	327	242,178	22.7
15	IL7RαDef	394	1	M-M→F	614	NA	No	103	197	0	Yes	530	221	255	13.0	54.4	119	151	184,906	11.96
16	IL7RαDef	322	1	F-F→F	210	NA	No	0	178	0	Yes	1095	736	336	52.4	20.6	6,010	293	177,138	7.55
17	IL7RαDef	12	2	F-F-M→M	254	154	No	29	76	1	Yes	646	283	320	60.5	22.3	<100	128	142,342	3.68
18	Jak3Def	238	1	F-F→M	3129	NA	No	0	83	1	Yes	926	339	490	22.9	40.7	126	785	260,860	27.2
19	Jak3Def	334	2	M-M-C→F	317	195	Yes	139	277	0	Yes	7466	5097	2063	77.6	9.8	2,740	847	203,595	16.9
20	Jak3Def	165	2	M-M-F→F	203	196	Yes	97	64	0	Yes	1446	765	575	61.1	14.1	14,000	247	160,328	8.2
21	X-linked	45	2	F-F-F→M	4869	532	No	0	16	1	Yes	4136	937	3372	3.8	86.0	874	84	29,118	27.1
22	X-linked	217	1	F-F→M	6941	NA	No	38	46	1	Yes	1588	620	920	14.7	56.2	<100	98	60,076	24.8
23	X-linked	175	2	M-M-M→M	131	4823	No	0	13	1	Yes	1851	433	1368	10.6	65.0	<100	97	87,139	19.4
24	X-linked	289	3	F-M-F-M→M	146	796	Yes	12	176	0	Yes	824	532	231	35.5	28.6	<100	292	157,805	19.0
25	X-linked	367	2	F-F-F→M	1304	1827	No	0	8	1	Yes	290	187	101	3.8	82.3	<100	175	28,448	17.2
26	X-linked	351	1	F-F→M	1641	NA	No	12	49	1	Yes	839	573	259	30.3	50	<100	876	212,320	16.8
27	X-linked	10	1	M-M→M	238	NA	No	0	25	1	Yes	1827	387	1289	19.4	40.5	<100	318	85,519	16.7
28	X-linked	163	1	F-C→M	141	NA	Yes	76	162	0	Yes	1749	691	862	54.2	23.9	N.D.	179	181,497	16.0
29	X-linked	224	1	F-F→M	182	NA	No	0	105	1	Yes	2047	1146	798	55.0	11.3	7410	2,658	112,410	9.82
30	X-linked	110	1	F-F→M	1750	NA	No	0	19	1	Yes	1140	447	604	35.5	36.4	352	128	212,632	8.88

Pat. No.	SCID Type	Age (da) 1st Trans*	# Boosts	D→R Sex**	Days to 1st Boost	Days to Last Boost	Donor B cells	mg/dl IgA	mg/dl IgM	IG RX***	Donor T Cells	#/cmm CD3	#/cmm CD4	#/cmm CD8	% CD3+ CD45RA+	% CD3+ CD45RO+	TREC μg/ml	Medium CPM	PHA CPM	Yrs Post Trans*
31	X-linked	260	3	F-F-M-M→M	322	700	No	17	66	1	Yes	59	47	11	5.3	79.3	<100	282	55,454	7.09
	Medians	**171**	**2**		**322**	**701**		**5**	**46**			**824**	**387**	**259**	**15**	**54**	**906**	**203**	**87,139**	**15**
	Means	**194**	**2**		**1,262**	**1,081**	5/31	**34**	**69**	22/31	28/31	**1,172**	**570**	**555**	**26**	**50**	**3,071**	**580**	**111,492**	**15**
	Deceased																			
32	ADADef	255	1	F-F→M	276	NA	No	388	42	1	Yes	1150	129	254	ND	ND	ND	258	321	3.56
33	ADADef	250	1	M-M→F	340	NA	No	149	94	1	0	375	97	277	22.5	67.9	151	467	45,445	18.27
34	ADADef	140	1	F-F→M	196	NA	No	0	0	1	0	127	63	ND	1.7	72.9	ND	2,621	10,833	0.58
35	AutoRec	198	3	M-F-F-C→F	138	252	No	0	0	1	Yes	8	10	2	50.0	10.0	ND	1084	1,179	1.72
36	AutoRec	181	1	F-F→F	1271	NA	No	0	0	1	Yes	290	235	52	5.1	80.4	36	99	56,795	12.36
37	AutoRec	447	1	F-M→F	159	NA	No	2	18	1	0	75	46	23	0.0	74.7	ND	235	8,123	0.88
38	Cd3ζDef	395	3	F-F-M-M→F	105	651	No	62	70	1	0	9	102	192	25.5	14.8	ND	87	2,264	6.95
39	RAG2Def	109	2	F-F-F→M	161	751	No	0	0	1	0	186	58	169	10.6	92.3	ND	4,565	11,511	3.16
40	IL7RaDef	199	1	F-F→M	117	NA	No	0	18	1	0	11	10	48	ND	ND	ND	1,231	1,282	0.3
41	IL7RaDef	559	3	F-F-M-F→M	91	266	No	54	318	1	0	55	5	102	1.0	88.5	0	766	2,873	2.0
42	IL7RaDef	162	2	F-F-M→M	154	91	No	8	32	1	0	5	3	18	25.8	9.7	ND	223	1,853	0.8
43	Jak3Def	448	2	F-F-G-→M	161	119	No	0	48	1	0	4	2	2	40.8	30.8	0	250	494	1.9
44	X-linked	597	2	F-F-F→M	208	558	No	0	2	1	0	15	117	11	ND	ND	ND	1061	1557	2.4
45	X-linked	194	2	F-F-C→M	543	51	No	67	186	1	Yes	34	18	18	37.1	50.4	ND	7710	138,608	2.0
46	X-linked	222	1	F-F→M	987	NA	No	0	415	1	Yes	1341	212	973	5.8	50.6	0	391	27,005	4.6
47	X-linked	147	1	F-F→M	357	NA	Yes	156	1570	1	Yes	8406	1562	4250	0.1	88.4	ND	466	26,564	1.2
48	Unknown	220	1	F-F→M	483	NA	No	11	0	1	0	35	24	28	7.5	84.6	ND	594	35184	4.2
49	Unknown	190	4	F-M-F-M-C→M	124	323	No	17	25	1	0	182	ND	ND	11.7	44.7	ND	986	8,714	2.2
	Medians	**210**	**2**		**179**	**266**		**5**	**29**			**65**	**58**	**50**	**11**	**68**		**531**	**8,419**	**2**
	Means	**273**	**2**		**326**	**340**	1/18	**51**	**158**	18	6/18	**684**	**158**	**401**	**16**	**57**		**1,283**	**21,145**	**4**
		p=0.04			**p=0.02**	**p= 0.03**						**p=0.0003**	**p<0.0001**	**p=0.02**	**p=0.13**				**p<0.0001**	**p<0.0001**

* Trans=first transplant

** F=female, M=male, C=unrelated cord, G=gene therapy

*** IG RX=immunoglobulin treatment, 1=Yes