

Letter to the Editor

Successful haploidentical bone marrow transplantation in a patient with reticular dysgenesis: 3-year follow-up

To the Editor:

Reticular dysgenesis (RD) is a rare form of severe combined immune deficiency (SCID) that presents earlier with failure to thrive, vomiting, diarrhea, and/or localized infection. Leukopenia and neutropenia unresponsive to granulocyte colony-stimulating factor are hallmarks, and the clinical course is rapidly fatal without intervention. These patients must be identified before transplantation because successful engraftment requires conditioning. We report a case of a successful haploidentical transplantation in a patient with RD. This patient was conditioned with busulfan, cyclophosphamide, and antithymocyte globulin. The patient is now 3 years from transplantation and has complete hematopoietic and immunologic reconstitution.

RD, first described in 1959 in male twins by Deval and Seynhaeve¹ is one of the most unusual and rapidly progressive forms of SCID, accounting for less than 1% of cases.² A deficiency of granulocyte precursors in the bone marrow, likely caused by a block in myeloid differentiation, is observed in RD. The pathogenesis is unknown; however, a defect that affects both lymphoid and myeloid precursors is presumed. Patients characteristically demonstrate marked leukopenia and a dysplastic thymus. Other manifestations can include thrombocytopenia and sensory deafness.³

In X-linked SCID successful transplantations without conditioning result in T-lymphocyte engraftment. However, in RD successful bone marrow transplantations seem to require intensive conditioning.⁴ In one case series of 10 patients who received HLA-nonidentical bone marrow transplantations for RD, 5 received myeloablative conditioning therapy with busulfan and cyclophosphamide, and of these, 3 are alive and well. The other 5 who received alternate conditioning regimens or no conditioning did not survive.⁴ Therefore differentiating these patients from those with other types of SCID is necessary to ensure optimal therapy.

Our patient presented to his pediatrician at 5 days of life with increased sleepiness and a rectal temperature of 104°F. Initial laboratory studies revealed a white blood cell count of 300 cells/ μ L and an absolute neutrophil count (ANC) of 0 cells/ μ L. Blood, urine, and cerebrospinal fluid cultures were obtained, and treatment with ampicillin, gentamicin, and acyclovir was initiated. He remained febrile and neutropenic despite treatment with granulocyte colony-stimulating factor. On day of life 8, he was transferred to the Children's Hospital of Philadelphia for additional evaluation and therapy.

The physical examination was remarkable for a warm purple area of induration around a heel puncture site and mild erythema at the circumcision site. At that time, the patient's white blood cell count was 600 cells/ μ L, with an absolute lymphocyte count of 180 cells/ μ L and an ANC of

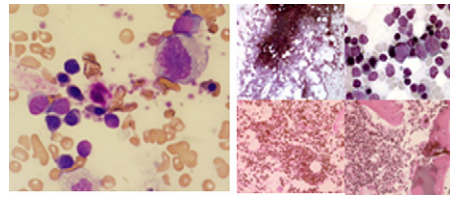


FIG 1. Pretransplantation and posttransplantation bone marrow cellularities. Initial bone marrow aspirate (*left*, $\times 60$ magnification) shows hypocellular marrow with erythroid precursors, rare myeloid precursors, and scattered maturing lymphocytes and macrophages. At *right*, bone marrow aspirate ($\times 4$ and $\times 50$ magnification) and a biopsy specimen ($\times 40$ magnification) show normocellular marrow with myeloid hypoplasia, normal erythroid and megakaryocyte maturation, and increased numbers of maturing lymphocytes.

0 cells/ μ L. His immunoglobulin levels were as follows: IgG, 556 mg/dL; IgA, less than 6 mg/dL; IgM, less than 4 mg/dL; and IgE, less than 5 IU/mL. The thymic shadow was absent on chest radiographic scanning but detectable on ultrasonographic analysis (see Fig E1 in the Online Repository at www.jacionline.org).

A pretransplantation bone marrow aspirate, performed at 12 days of age, revealed hypocellular-for-age marrow with rare myeloid precursors and markedly decreased lymphocytes (Fig 1, left). Flow cytometric analysis confirmed the histologic findings and showed the lymphocytes were mostly maturing B cells.

A diagnosis of RD was made, and conditioning was begun on day 19 of life. He received intravenous busulfan with pharmacokinetics, cyclophosphamide (200 mg), and thymoglobulin (9 mg). The donor was his haploidentical mother. Mobilized peripheral stem cells were T depleted with CD34⁺ selection by using Isolex (Nexell Therapeutics, Irvine, Calif). Initially, he received 10×10^6 /kg CD34⁺ cells and 1.9×10^4 /kg CD3⁺ cells. He was boosted 7 months later because of neutropenia with 2.2×10^6 /kg CD34⁺ cells and 2.5×10^3 /kg CD3⁺ cells. There was no graft-versus-host disease (GVHD; see Fig E2 in the Online Repository at www.jacionline.org for engraftment timeline).

A bone marrow aspirate and biopsy, performed 6 months after transplantation, showed normocellular-for-age marrow with granulocytic hypoplasia and increased numbers of maturing lymphocytes (Fig 1, right).

Twenty months after transplantation, our patient had a white blood cell count of 5800 cells/ μ L, with an ANC of 928 cells/ μ L and an absolute lymphocyte count of 4698 cells/ μ L. Cell-surface markers showed a CD3⁺ count of 4252 cells/ μ L, a CD3⁺/CD4⁺ count of 2560 cells/ μ L, a CD3⁺/CD8⁺ count of 1466 cells/ μ L, a CD3⁺/CD16⁺/CD56⁺ count of 287 cells/ μ L, a CD45RA⁺ count of 2039 cells/ μ L, and a CD45RO⁺ count of 324 cells/ μ L. There was normal lymphocyte proliferation in response to mitogens at 20 months after transplantation (see Table E1 in the Online Repository at www.jacionline.org).

TABLE I. Bone marrow transplantation for RD

First author/center	No. of RD cases	Conditioning	HLA match and source	Outcome
Reubsat et al, ⁵ Wilhelmina Children's Hospital, Utrecht, The Netherlands	1	First: treosulfan, 500 mg/kg/d $\times$ 3 d; fludarabine, 25 mg/m ² /d $\times$ 4 d; Second: busulfan, 320 mg/m ² ; cyclophosphamide, 200 mg/kg plus, ATG, 10 mg/kg	6/6 match cord blood followed by 5/6 matched unrelated cord blood	Well 1 y after second transplantation
Bhattacharya et al, ⁶ Newcastle General Hospital, United Kingdom, May 2000-2004	1	Alemtuzumab; busulfan, 16 mg/kg; cyclophosphamide 200	10/10 cord blood	100% donor chimerism; mean follow-up, 2 y
Antoine et al, ⁷ European Bone Marrow Registry, 1968-1999	12	If given: busulfan, 8 mg/kg; cyclophosphamide, 200 mg/kg	n = 2, genotypically HLA identical; n = 1, phenotypically HLA identical; n = 8, HLA mismatched; n = 1, unrelated	RD 3-y survival: 75% matched, 29% mismatched (all patients with RD who survived received a myeloablative CR; Fischer, personal communication)
Bertrand et al, ⁴ Ulm, Paris, London; EBMT/ ESID, 1979-1999	10	Busulfan, 8 mg/kg; busulfan, 16 mg/kg, and cyclophosphamide, 200 mg/kg; or cyclophosphamide and ATG	Nonidentical (15 HSCTs, 10 = from mothers, 3 = fathers, 1 = both parents)	3/10 survivors; only patients receiving busulfan, 16 mg/kg, plus cyclophosphamide survived
Knutsen and Wall, ⁸ Cardinal Glennon Children's Hospital, St Louis University	1	Busulfan, 1 mg/kg every 6 h on day -9 to day -6; cyclophosphamide, 50 mg/kg, on day -5 to day -2; ATG, 30 mg/kg, on day -3 to day -1, then TBI/ cyclophosphamide/ATG plus GVH prophylaxis and second donor infusion	Unrelated cord blood $\times$ 2	Alive and well
Haddad et al, ⁹ European Bone Marrow Registry, 1982-1993	6	n = 27 received no conditioning; n = 18 received cyclophosphamide, 200 mg/kg; n = 2 received cyclophosphamide and ATG; n = 2 received ATG only; n = 4 received busulfan, 8 mg/kg; n = 44 received busulfan, 8 mg/kg and cyclophosphamide; n = 25 received busulfan, 16 mg/kg and cyclophosphamide; n = 4 unknown	HLA-nonidentical related donor (parents with HLA 1 antigen to full haplotype mismatch)	4 alive with donor T-cell engraftment at 6 mo BMT; 2 alive at last follow-up (median, 6 y)
DeSantes et al, ¹⁰ UCSF	2	n = 1, ATG; n = 1 ATG, cyclophosphamide and busulfan, cyclophosphamide, ATG	T-depleted haploidentical	Failed engraftment until after TBI with or without other agents

ATG, Antithymocyte globulin; CR, conditioning regimen; EBMT/ESID, European Group for Blood and Marrow Transplantation/European Society for Immunodeficiencies; HSCTs, hematopoietic stem cell transplants; TBI, total body irradiation; GVH, graft versus host.

Intravenous immune globulin was discontinued 20 months after transplantation. The results of hearing studies have been normal.

This case illustrates several important features of RD that differentiate it from other forms of SCID. Our patient presented at 5 days of life, and his initial blood work showed profound leukopenia with severe lymphopenia and neutropenia, which are consistent with previously described cases of RD. He did not have thrombocytopenia or deafness.

As with all forms of SCID, RD is treated with hematopoietic stem cell transplantation. Patients with RD appear to do better with more intensive conditioning

before transplantation. We have reviewed the literature specifically mentioning regimens and outcomes for RD (Table I).⁴⁻¹⁰ Patients who received conditioning, specifically with busulfan (16 mg/kg) and cyclophosphamide, had better engraftment and survival than patients who did not. Unrelated cord blood or haploidentical transplantation has been successful. Because RD is so rare and its presentation is earlier than that of other forms of SCID, differentiating RD from other causes of neutropenia and SCID is crucial so that more aggressive conditioning before bone marrow transplantation can be instituted. This case adds to the small number of published reports

regarding the treatment and outcomes of RD and further supports the use of myeloablative pretransplantation conditioning for the treatment of RD.

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TABLE E1. Immunologic studies over time

	8 d	12 d	4 mo	5 mo	7 mo	19.5 mo	20.5 mo	24 mo
Cell subsets (cells/ μ L)								
WBC	1300	600	2500	2600	1900	7100	5800	8200
ANC	0	0	1150	770	38	213	928	—
ALC	—	180	1100	1742	1824	6532	4698	—
CD3 ⁺	—	122	128	695	1113	5830	4252	—
CD3 ⁺ /CD4 ⁺	—	96	70	500	793	3493	2560	—
CD3 ⁺ /CD8 ⁺	—	18.7	13	118	255	2001	1466	—
CD3 ⁺ /CD16 ⁺ /CD56 ⁺	—	23.4	596	606	529	522	287	—
CD20 ⁺	—	23	128	413	137	225	132	—
CD5 ⁺ /CD19 ⁺	—	—	—	—	53	79	—	—
CD4 ⁺ /CD45RA ⁺	—	—	48	320	584	3150	2039	—
CD4 ⁺ /CD45RO ⁺	—	—	58	179	219	310	324	—
Immunoglobulins (mg/dL)								
IgG	—	556	605	642	—	—	617	491
IgA	—	—	—	—	—	—	—	21
IgM	—	—	—	—	—	—	—	69
Vaccine titers (IU/mL)								
Tetanus	—	—	—	—	—	—	—	0.9 (>0.6)
Diphtheria	—	—	—	—	—	—	—	1.5 (>0.1)
Pneumococcal	—	—	—	—	—	—	—	2/14
Mitogens (SI _{pt} [SI _{cont}])								
PHA	—	—	—	—	—	—	1263 (217)	—
PWM	—	—	—	—	—	—	1369 (134)	—
ConA	—	—	—	—	—	—	1082 (161)	—

ALC, Absolute lymphocyte count; *SI_{pt}*, Stimulation Index for patient; *SI_{cont}*, Stimulation Index for control; *PHA*, phytohemagglutinin; *PWM*, pokeweed mitogen; *ConA*, concanavalin A.

Pneumococcal antibodies shown as number of serotypes protective out of 14 tested.

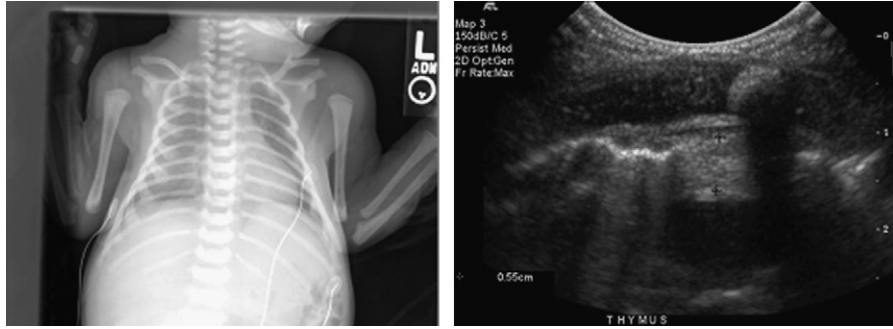


FIG E1. Chest x-ray film shows absent thymus. Ultrasonographic analysis (not shown) showed a small thymus measuring 2.9 cm (normal, 3.5 cm).

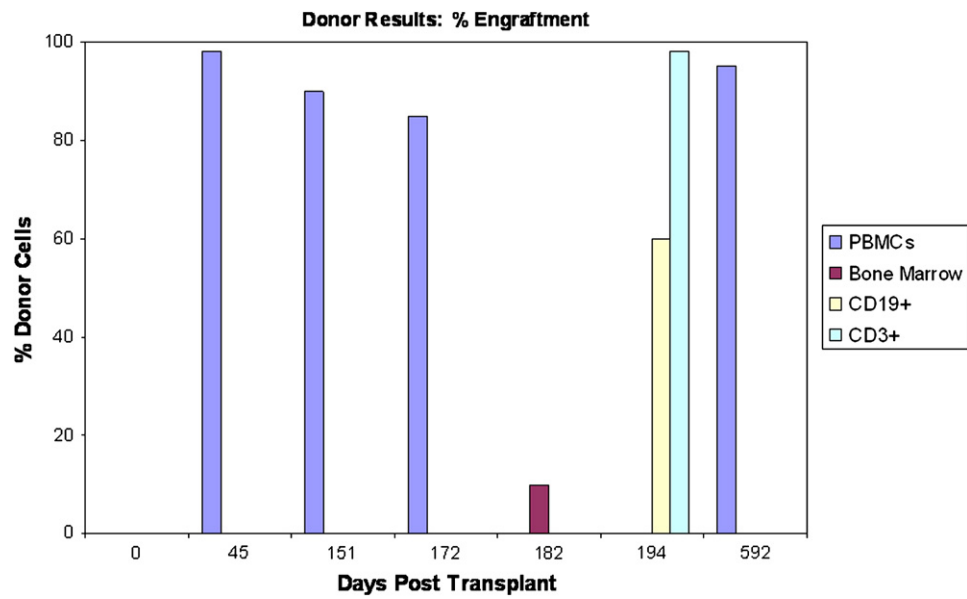


FIG E2. Over time, the patient shows peripheral engraftment of his CD3 (T cells) and CD19 (B cells) cells. As is commonly seen after transplantation, the T cells achieve better engraftment. The lower engraftment in the bone marrow reflects the fact that the aspirate used to obtain that sample is likely mixed with other cell lines.