ARTICLE

Allogeneic Hematopoietic Stem-Cell Transplantation for Leukocyte Adhesion Deficiency

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What's Known on This Subject

Leukocyte Adhesion Deficiency is a rare inherited immune disorder characterized by defective immune cell migration. Bone marrow and peripheral blood stem cell transplantation offers the possibility of cure, but can be associated with significant complications.

What This Study Adds

Hematopoietic stem cell transplantation is advocated in LAD, especially when suitable HLA-matched donors are available. Matched unrelated donor transplants can be successful in combination with less toxic, reduced intensity conditioning regimens. Haploidentical transplants should be procedures of last resort.

ABSTRACT

OBJECTIVES. Leukocyte adhesion deficiency is a rare primary immune disorder caused by defects of the CD18 β-integrin molecule on immune cells. The condition usually presents in early infancy and is characterized by deep tissue infections, leukocytosis with impaired formation of pus, and delayed wound healing. Allogeneic hematopoietic stem-cell transplantation offers the possibility of curative therapy, and with patient numbers at any individual center being limited, we surveyed the transplant experience at 14 centers worldwide.

METHODS. The course of 36 children with a confirmed diagnosis of leukocyte adhesion deficiency who underwent hematopoietic stem-cell transplantation between 1993 and 2007 was retrospectively analyzed. Data were collected by the registries of the European Society for Immunodeficiencies/European Group for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research.

RESULTS. At a median follow-up of 62 months (extending to 14 years), the overall survival rate was 75%. Myeloablative conditioning regimens were used in 28 patients, and reduced-intensity conditioning in 8 patients, with no deaths in this subgroup. Survival rates after matched family donor and unrelated donor transplants were similar, with 11 of 14 matched family donor and 12 of 14 unrelated donor recipients alive; mortality was greatest after haploidentical transplants, after which 4 of 8 children did not survive. Twenty-seven transplant recipients were alive, with full donor engraftment in 17 cases, mixed multilineage chimerism in 7 patients, and mononuclear cell-restricted chimerism in an additional 3 cases.

CONCLUSIONS. Hematopoietic stem-cell transplantation offers long-term benefit in leukocyte adhesion deficiency and should be considered as an early therapeutic option if a suitable HLA-matched stem-cell donation is available. Reduced-intensity conditioning was particularly safe, and mixed-donor chimerism seems sufficient to prevent significant symptoms, although careful long-term monitoring will be required for these patients. *Pediatrics* 2009;123:836–840

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Key Words
leukocyte adhesion deficiency, stem-cell transplantation, reduced-intensity conditioning

Abbreviations
ATG—antithymocyte globulin
CLAD—canine leukocyte adhesion deficiency
CMV—cytomegalovirus
EBV—Epstein-Barr virus
GVHD—graft-versus-host disease
HSCT—hematopoietic stem-cell transplantation
LAD—leukocyte adhesion deficiency
LFA-1—lymphocyte function associated antigen-1
MFD—matched family donor
PBSC—peripheral blood stem-cell collection
RIC—reduced-intensity conditioning

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LEUKOCYTE ADHESION DEFICIENCY (LAD) type 1 is a rare autosomal recessive immunodeficiency documented in ~300 patients worldwide. Defective expression of the β-2 integrin, CD18, on immune cells results in impaired leukocyte

adhesion, egression, and migration. CD18 forms the dimeric complexes lymphocyte function associated antigen-1 (LFA-1) in association with CD11a, Mac-1 in combination with CD11b, and p150-95 with CD11c. These molecular complexes are essential for effective migration and homing of immune cells, including neutrophils, dendritic cells, and T lymphocytes.[1,2] Defective neutrophil migration can result in omphalitis and delayed separation of the umbilical cord, a characteristic and early presenting hallmark of LAD1.[3] Other features include recurrent deep tissue bacterial infections affecting the skin and mucosa. Leukocytosis in peripheral blood and the absence of pus formation at sites of infection is characteristic. Poor postoperative wound healing may be a presenting feature. Patients with <1% CD18 expression are considered to have the most severe phenotype, with serious infections leading to life-threatening complications in early infancy. Allogeneic hematopoietic stem-cell transplantation (HSCT) offers the possibility of curative therapy for LAD, but, as the condition is extremely rare, experience at any particular center is limited.[4,5] A 2-center study has previously reported the outcomes of 14 matched-family and haploidentical donor transplants, undertaken between 1982 and 1993. The findings noted particular difficulties associated with transplantation for LAD, including graft rejection and graft-versus-host disease (GVHD). In some patients, additional chemotherapy with agents such as etoposide was used to supplement conventional myeloablative conditioning with busulphan and cyclophosphamide.[6] There was an overall mortality rate of 28%, but interestingly no difference in survival rate after HLA-identical or nonidentical procedures was detected, and the study has broadly influenced the subsequent approach to stem-cell transplantation for LAD. We surveyed the results of transplantation undertaken in the subsequent period, between 1993 and 2007, of children who were treated at 14 centers worldwide and have compiled a series of 36 patients. Our findings provide the most comprehensive picture of outcomes after transplantation and highlight an increased use of alternative stem-cell sources and reduced-intensity regimens.

PATIENTS AND METHODS

Data Sources

Patient data, transplant characteristics, and outcomes were reported to the European Society for Immunodeficiencies/European Group for Blood and Marrow Transplantation registry and the Center for International Blood and Marrow Transplant Research. Fourteen centers treated between 1 and 9 patients each (median: 1.5 per center). Included are patients documented as having reduced or absent expression of CD18 by flow-cytometric analysis and transplanted after 1993. Excluded are patients with a clinical suspicion of LAD but without proven reduction in CD18 expression. Although this is the largest series to date, patients treated under identical transplant regimens were small, limiting the power of any statistical analysis.

Transplantation

Thirty-six patients underwent their first transplant for LAD between 1993 and 2007. Patients received bone marrow ($n = 27$), peripheral blood progenitor cells ($n = 4$), or umbilical cord blood grafts ($n = 5$) from 14 HLA-matched family donors, 8 haploidentical donors, and 14 unrelated donors (Table 1). The median age at stem-cell transplantation was 9 months (range: 2 months to 14 years). Most patients ($n = 28$) received fully myeloablative regimens with combinations of busulphan (16–20 mg/kg), cyclophosphamide (100–200 mg/kg), and etoposide (900 mg/m^2). Additional serotherapy included Campath 1G, anti-LFA-1, anti-CD2 antibody, anti-CD3 antibody, or antithymocyte globulin (ATG). The remaining 8 patients received reduced-intensity conditioning (RIC) with combinations of fludarabine (150 mg/m^2), melphalan (140 mg/m^2), treosulphan (42 mg/m^2), Campath 1H (1 mg/kg), and rabbit ATG (10 mg/kg). In the haploidentical setting, T-cell depletion was achieved by E-Rosetting or CD34$^+$ stem-cell selection from marrow or mobilized peripheral blood stem-cell collection (PBSC). Most patients received cyclosporine either alone or in combination with mycophenolate, methotrexate and/or prednisolone for GVHD prophylaxis. Chimerism after stem-cell transplantation was monitored by a variety of techniques including fluorescent in situ hybridization for gender mismatched grafts, polymerase chain reaction analysis using microsatellite probes, and flow cytometry for CD18.[7,8] Six patients received a second stem-cell transplant for graft failure ($n = 5$) or secondary malignancy (Epstein-Barr virus [EBV] lymphoma, $n = 1$) and 2 patients underwent a third procedure for graft failure or low-level donor chimerism. All but 1 of these multiple grafts was in the haploidentical setting.

RESULTS

In general, outcomes after HSCT for primary immunodeficiencies have improved over time.[7] We found that the long-term survival rate after transplantation for LAD undertaken between 1993 and 2007 was ~75%; little changed from results reported for the period of 1982 through 1993.[6] Previous transplant experience had suggested that nonidentical, T-cell–depleted grafts could be as successful as HLA-identical procedures in LAD, but our survey found a high level of primary graft failure, which resulted in secondary (or tertiary) grafting in all 8 haploidentical transplants. Consequently, only 4 of 8 (50%) children in this subgroup survived. The increased availability of matched unrelated adult and cord blood stem-cell grafts has been an important change in recent years, and survival rates after either matched family donor or unrelated donor transplantation were notably better. Thus, 12 of 14 (86%) recipients of unrelated donor HSCT survived, and this was comparable to 11 of 14 (79%) of the matched family donor recipients.

Nine patients (4 haploidentical, 3 sibling donor, and 2 matched unrelated donor) did not survive after transplantation (Table 2). All had received myeloablative conditioning and donor engraftment was established in 7 patients, albeit after repeat procedures in 5 cases. Infection-related deaths occurred in 5 cases, with 3 deaths

TABLE 1 Patients Who Survived After Allogeneic Transplantation for LAD

	Donor	Age, mo	Year of BMT	Follow-up, mo	Conditioning	Graft	Prophylaxis	GVHD	Infections	Chimerism
1	MFD	14	1996	156	Bu CY VP16	BM	CyA Mtx	III/IV		Full
2	MFD	18	2006	14	Flu Mel Cam1H[a]	BM	CyA MMF	II	CMV	MNC 30
3	MFD	3	2007	5	Flu Treo Cam1H[a]	BM	CyA MMF			Full
4	MSD	78	1994	156	Bu CY VP16	UCB	CyA Mtx		Pneumonitis	PMN 44 MNC 64
5	MSD	10	1995	147	Bu CY VP16	BM	CyA		EBV	Full
6	MSD	6	1997	120	Bu CY	BM	CyA	II		MNC 100
7	MSD	2	2000	36	Bu Cy	BM	CyA Mtx Prd			Full
8	MSD	5	2003	36	Bu CY	BM	CyA			Full
9	MSD	4	2003	36	Bu CY ATG	BM	CyA			Full
10	MSD	16	2005	30	Bu Cy ATG	BM	CyA Mtx Prd		CMV	PMN 25 MNC 77
11	MSD	11	2006	24	Bu CY	BM	CyA	I		Full
12	MUD	8	1993	168	Bu CY Cam1G	BM	CyA Mtx			Full
13	MUD	150	1998	71	Bu CY VP16	BM	CyA Mtx		VZV	PMN 63 MNC75
14	MUD	60	2000	72	Flu Mel Cam1H[a]	BM	CyA		CMV, EBV	PMN100 MNC92
15	MUD	24	2001	72	Flu Mel Cam1H[a]	BM	CyA	II/III	ADV	Full
16	MUD	36	2001	74	Flu Mel Cam1H[a]	BM	CyA		Crypto	PMN 87 MNC 93
17	MUD	24	2003	62	Flu Mel Cam1H[a]	BM	CyA			Full
18	MUD	8	2006	24	Bu CY ATG	BM/CD34		II		MNC 30
19	MUD 1AMM	9	2006	14	Flu Treo Cam1H[a]	BM	CyA MMF	III/IV	CMV, fungal	Full
20	MUD 1AMM	27	1999	96	Bu CY ATG	UCB	CyA Prd			Full
21	MUD 1AMM	4	1999	50	Bu CY ATG	UCB	CyA Prd	I/II		Full
22	MUD 3AMM	7	2007	12	Flu Treo ATG[a]	UCB	CyA Prd			PMN 3 MNC 5
23	MUD 3AMM	7	1997	93	Bu CY ATG	UCB	CyA Prd	I	Candida	Full
24	(*i*) HAPL	7	1999	96	(*i*) Bu CY TP	(*i*)BM/CD34		I		Full
	(*ii*) HAPL				(*ii*) Flu Mel ATG	(*ii*) BM/CD34				
25	(*i*) HAPL(P)	2	2000	19	(*i*) Bu CY ATG	(*i*) PBSC/CD34				Full
	(*ii*) HAPL(M)				(*ii*) Flu aCD3	(*ii*) PBSC/CD34				
	(*iii*) HAPL(M)				(*iii*) None	(*iii*) PBSC/CD34				
26	(*i*) HAPL	22	2003	48	(*i*) Bu CY ATG	(*i*) PBSC/CD34		III		Full
	(*ii*) HAPL				(*ii*) Flu Mel TP Cam1G	(*ii*) PBSC/CD34				
27	(*i*) HAPL	4	1993	147	(*i*) Bu CY ATG	(*i*) BM T dep	CyA		Candida	PMN 24, MNC10
	(*ii*) MMFD				(*ii*) TBI CY ARA-C	(*ii*) BM T dep				

AMM indicates antigen mismatched; ARA-C, cytarabine; ARDS, acute respiratory distress syndrome; BM, bone marrow; BMT, bone marrow transplantation; Bu, busulphan; Cam1G, Campath 1G; Cam1H, Campath 1H; CY, cyclophosphamide; CyA, cyclosporin; Flu Mel, Fludarabine, Melphalan; Flu Treo, Fludarabine, Treosulphan; HAPL, haploidentical donor (P, paternal; M, maternal); MMFD, mismatched family donor; MSD, matched sibling donor; MUD, matched unrelated donor; MNC, mononuclear cells; Mtx, methotrexate; MMF, mycophenolate mofetil; PBSC, peripheral blood stem cell collection (CD34 selected where indicated); PMN, polymorphonuclear cells; Prd, prednisolone; TBI, total body irradiation; T dep, T-cell depleted; TP, thiopeta; UCB, umbilical cord blood; VOD, veno-occlusive disease; VP16, etoposide; VZV, varicella zoster virus.

[a] Indicates RIC.

linked to veno-occlusive disease and 1 case of secondary malignancy (EBV lymphoma). We noted that 6 deaths occurred in the first 7-year period of this analysis (1993–2000) compared with 3 deaths in the subsequent period (2001–2007). This probably reflects the reduced use of haploidentical donors in the second period, rather than any generalized improvements in transplantation procedures or supportive care in recent years.

Complications that may be anticipated after allogeneic stem-cell transplantation include GVHD, infections, and the toxic adverse effects of chemotherapy. Nine patients developed GVHD at grade II or greater, including 2 cases of severe grade IV skin and gut GVHD (1 matched family donor [MFD] and the other a 1-antigen mismatched unrelated donor). Viral reactivations of cytomegalovirus (CMV), EBV, adenovirus, and varicella zoster were detected, and there were at least 2 significant cases of unexplained pneumonitis. Veno-occlusive disease in 3 cases followed busulphan-based conditioning and contributed to the cause of death in these cases. Overall, the use of RIC regimens seemed to be associated with reduced toxicity, with all 8 patients in this subgroup surviving, although 2 (patients number 2 and 22) had low-level donor chimerism. With 27 surviving patients followed-up for a median of 62 months, full chimerism was recorded in 17 patients, with stable mixed chimerism in granulocytes and mononuclear cells being achieved in 7 patients (Table 1). The latter included an umbilical cord blood graft recipient mismatched at 3-loci who had very low levels of chimerism in both lineages (~5%) but remained symptom free. The remaining 3 patients had lymphoid engraftment (1 full, 2 mixed) but no documented engraftment of donor granulocytes, and these patients also remained well but continued to receive close monitoring.

DISCUSSION

We report the transplant experience for LAD for procedures undertaken at 14 centers worldwide over a 14-year period. There is general agreement that infants presenting with significant infections in the first weeks or months of life who have a diagnosis of LAD confirmed

TABLE 2 Patients not Surviving After Allogeneic Transplantation for LAD

	Donor	Age, mo	Year BMT	Conditioning	Graft	GVHD Prophylaxis	GVHD Grade	Engraftment	Cause of Death
1	MSD	15	1995	Bu VP16	BM	Mtx		Yes	Pneumonitis
2	MSD	3	2001	Bu CY	BM	CyA		Yes	VOD
3	MSD	8	2001	Bu CY	BM	CyA Mtx Prd		Yes	VOD
4	MUD	168	1996	Bu CY Cam1G	BM	CyA Mtx		Yes	Infection
5	(*i*) MUD	13	1998	(*i*) Bu CY ATG	(*i*) BM	CyA Mtx	II	Yes	Infection
	(*ii*) MUD			(*ii*) Bu CY VP16 ATG	(*ii*) BM				
6	(*i*) HAPL	19	1993	(*i*) Bu CY VP16	(*i*) BM T dep	CyA	I	No	Infection, malignancy
	(*ii*) MUD			(*ii*) TBI CY ATG	(*ii*) BM				
7	(*i*) HAPL(P)	5	1994	(*i*) Bu CY VP16 α LFA-1 α CD2	(*i*) BM T dep			Yes	Infection
	(*ii*) HAPL(M)			(*ii*) Bu CY VP16 Cam1G	(*ii*) BM T dep				VOD
8	(*i*) HAPL(P)	3	1997	(*i*) Bu CY α CD2	(*i*) BM T dep	CyA		Yes	Infection
	(*ii*) HAPL(M)			(*ii*) Bu CY α CD2 ATG	(*ii*) BM T dep				
	(*iii*) HAPL(M)			(*iii*) CY ATG	(*iii*) BM T dep				
9	(*i*) HAPL(M)	4	2004	(*i*) Bu CY ATG	(*i*) BM T dep			No	ARDS
	(*ii*) HAPL(P)			(*ii*) Bu CY ATG	(*ii*) PBSC/CD34				

ARDS indicates acute respiratory distress syndrome; BM, bone marrow; Bu, busulphan; Cam1G, Campath 1G; CY, cyclophosphamide; CyA, cyclosporine; HAPL, haploidentical donor (P, paternal; M, maternal); MSD, matched sibling donor; MUD, matched unrelated donor; Mtx, methotrexate; PBSC, peripheral blood stem cell collection (CD34 selected where indicated); Prd, prednisolone; T dep, T-cell depleted; VOD, veno-occlusive disease; VP16, etoposide.

on the basis of CD18 expression should undergo early HSCT if a suitable HLA-matched family donor can be identified. In the absence of a HLA-matched family donor, the ready availability of a parental haploidentical donor has obvious attractions, and previous experience of successful haploidentical transplantation in LAD has suggested that T-cell–depleted family mismatched grafts could be as successful as HLA-identical (T-cell replete) procedures in LAD. It was postulated that this may relate to the reduced ability of the LAD host to mediate graft rejection.[5,6] This observation has not been borne out in the current series, where all the haploidentical grafts were initially rejected despite full myeloablative conditioning. Secondary procedures were performed by using either the same (2 cases) or alternative donors (6 cases), resulting in successful reconstitution in 4 patients. This experience is in line with that seen for other primary immune deficiencies treated using HLA-mismatched donors.[7] In such settings, the depletion of donor T cells necessary for preventing GVHD results in reduced graft potency, and increases the risk of graft failure and infective complications.[9]

In more recent years, there has been increased availability of unrelated volunteer donors and umbilical cord stem-cell donations, and this is reflected in our series, which included 14 such procedures. Until now there have been only isolated reports describing the successful transplantation for LAD using matched unrelated adult donors[10–14] and umbilical cord blood grafts.[15] As unrelated donor transplants undertaken with conventional myeloablative conditioning can be associated with significant toxicity, especially in the context of preexisting organ dysfunction, a number of these procedures were performed using modified, reduced-intensity regimens. We previously documented improved survival rates in children with primary immune deficiencies who underwent RIC procedures.[8] These transplants are generally less toxic and rely on intense immunosuppression to engineer host:donor tolerance sufficient for reliable donor engraftment. In the LAD setting, the RIC regimens were well tolerated, and although a number of children have mixed chimerism, all remain alive and free of significant symptoms. The long-term consequences of RIC preconditioning in these patients will be of particular interest considering that intact fertility and uncomplicated pregnancies have been reported in dogs with canine LAD (CLAD) after nonmyeloablative stem-cell transplantation.[16]

Interestingly, low levels of donor neutrophil engraftment as measured in peripheral blood seem sufficient for patients to remain symptom free. The minimum level of functional CD18 expression on leukocytes required to prevent complications is not known. Somatic reversion events, leading to normal CD18 expression on a small fraction of peripheral blood T cells, have been reported in LAD.[17,18] Somatic mosaicism in patients with other inherited immunodeficiencies has been linked to milder phenotypes,[19,20] but in LAD the reversion phenomena have been limited to $CD8^+$ T cells, and it is unclear if small populations of $CD18^+$ T cells played a role in patient survival into adulthood or if they arose as a consequence of longer-term survival.[17]

In addition, observations from animal studies are encouraging and suggest that low levels of functional, CD18-expressing leukocytes can prevent disease.[21] Transplant studies in CLAD have indicated that <500 $CD18^+$ donor neutrophils per μL in peripheral blood can reverse disease phenotype.[22] It should be noted that in LAD the levels of circulating donor neutrophils may not accurately reflect levels of true engraftment, as functional $CD18^+$ cells may preferentially egress the circulation and mediate important beneficial effects at target sites such as the oral mucosa. Thus, in dogs, selective accumulation of donor neutrophils was demonstrated in the oral mucosa resulting in significantly higher levels of donor chimerism in the saliva of animals compared with peripheral blood after transplantation.[22] Evidence from gene therapy studies in the CLAD model also supports

the notion that low numbers of functional cells can prevent disease. The infusion of autologous hematopoietic stem cells transduced to express canine CD18 corrected 5% to 10% of circulating leukocytes, and this was sufficient to mediate durable reversal of the disease.[23] Presently, a number of patients with mixed-donor chimerism, including those with only mononuclear lineage engraftment, remain free of significant disease. Additional investigation of these patients may be warranted, including detailed lineage-specific chimerism in tissues (in the bone marrow and gingival tissues) and the exclusion of host-mediated cellular or autoantibody responses against donor-derived cells.

CONCLUSIONS

LAD1 is a serious primary immune disorder that can be corrected by allogeneic HSCT. Matched family donor and unrelated donor procedures were equally successful and mixed chimerism in peripheral blood seems sufficient to keep patients free of significant symptoms. The study has highlighted the impressive safety profile of RIC regimens, and the greater availability of suitable unrelated donors in combination with tailored conditioning regimens should improve outcomes further.

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An error occurred in this article published in the January 2009 issue of *Pediatrics* (doi:10.1542/peds.2007-2680). The authors inadvertently omitted the list of participating centers, principal investigators, and research coordinators from the manuscript:

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An error occurred in this article published in the March 2009 issue of *Pediatrics* (doi:10.1542/peds.2008-1191). On page 836, in the authorship list, line 4 reads "Mary Slatten, MBBSr[i]." This should have read: "Mary Slatter, MBChB[i]."

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Allogeneic Hematopoietic Stem-Cell Transplantation for Leukocyte Adhesion Deficiency

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