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Allogeneic hematopoietic stem cell transplantation for Leukocyte Adhesion Deficiency

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Abstract

OBJECTIVES—Leukocyte Adhesion Deficiency (LAD) 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 characterised by deep tissue infections, leukocytosis with impaired formation of pus and delayed wound healing. Allogeneic haematopoietic stem cell transplantation (HSCT) offers the possibility of curative therapy, and with patient numbers at any individual centre being limited, we surveyed the transplant experience at 14 centres worldwide.

PATIENTS & METHODS—The course of 36 children with a confirmed diagnosis of LAD who underwent HSCT between 1993 and 2007 was retrospectively analysed. Data was collected by the registries of the European Society for Immunodeficiencies (ESID)/European Group for Blood and Marrow Transplantation (EBMT), and the Center for International Blood and Marrow Transplant Research (CIBMTR)

RESULTS—At median followup of 62 months (extending to 14 years) overall survival was 75%. Myeloablative conditioning regimens were used in 28 patients, and reduced intensity conditioning (RIC) in 8 patients, with no deaths in this subgroup. Survival after matched family donor and

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unrelated donor transplants was similar, with 11/14 matched family donor and 12/14 unrelated donor recipients alive; mortality was greatest following haplo-identical transplants, where 4/8 children did not survive. Twenty seven transplant recipients are alive, with full donor engraftment in 17 cases, mixed multi-lineage chimerism in 7 patients, and mononuclear cell restricted chimerism in a further 3 cases.

CONCLUSIONS—HSCT offers long term benefit in LAD 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 appears sufficient to prevent significant symptoms, although careful long term monitoring will be required for these patients.

Keywords

Leukocyte adhesion deficiency; Stem cell transplantation; Reduced Intensity Conditioning

INTRODUCTION

Leukocyte adhesion deficiency (LAD) type 1 is a rare autosomal recessive immunodeficiency documented in approximately 300 patients worldwide. Defective expression of the beta-2 integrin, CD18, on immune cells results in impaired leukocyte adhesion, egression and migration. CD18 forms the dimeric complexes LFA-1 (lymphocyte function associated antigen-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 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 post-operative wound healing may be a presenting feature. Patients with less than 1% CD18 expression are considered to have the most severe phenotype, with serious infections leading to life-threatening complications in early infancy. Allogeneic haematopoietic stem cell transplantation (HSCT) offers the possibility of curative therapy for LAD, but as the condition is extremely rare, experience at any particular centre is limited.^{4,5} A two centre study has previously reported the outcomes of 14 matched family and haploidentical donor transplants, undertaken between 1982-1993. Their 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 following HLA-identical or non-identical procedures was detected, and the study has broadly influenced the subsequent approach to stem cell transplantation for LAD. We have surveyed the results of transplantation undertaken in the subsequent period, between 1993 and 2007, of children who were treated at 14 centres worldwide and have compiled a series of 36 patients. Our findings provide the most comprehensive picture of outcomes following 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 (ESID)/European Group for Blood and Marrow Transplantation (EBMT) registry and the Center for International Blood and Marrow Transplant Research

(CIBMTR). Fourteen centres treated between 1-9 patients each (median 1.5/centre). 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 any one particular transplant regimen 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 1A, 1B). The median age at SCT was 9 months (range 2 months – 14 years). Most (n=28) patients received fully myeloablative regimens which combinations of Busulphan (16-20mg/kg), Cyclophosphamide (100-200mg/kg) and Etoposide (VP16, 900mg/m²). Additional serotherapy included Campath 1G, anti-leukocyte function antigen-1 (LFA-1), anti-CD2 antibody, anti-CD3 antibody, or anti-thymocyte globulin (ATG). The remaining 8 patients received reduced intensity conditioning (RIC) with combinations of Fludarabine (150mg/m²), Melphalan (140mg/m²), Treosulphan (42mg/m²), Campath 1H (1mg/kg) and rabbit ATG (10mg/kg). In the haploidentical setting T cell depletion was achieved by E-Rosetting or CD34⁺ stem cell selection form marrow or mobilised PBSC. Most patients received Cyclosporine either alone or in combination with Mycophenolate, Methotrexate and/or Prednisolone for graft-versus-host disease (GVHD) prophylaxis. Chimerism post-SCT was monitored by a variety of techniques including fluorescent in situ hybridisation (FISH) for sex mismatched grafts, PCR analysis using micro-satellite probes, and flow cytometry for CD18.^{7,8} Six patients received a second SCT for graft failure (n=5) or secondary malignancy (EBV lymphoma, n=1) and 2 patients underwent a third procedure for graft failure or low level donor chimerism. All but one of these multiple grafts was in the haploidentical setting.

RESULTS

In general, outcomes following HSCT for primary immunodeficiencies have improved over time.⁷ We found long term survival following transplantation for LAD undertaken between 1993-2007 was around 75%, little changed to that reported for the period 1982-1993.⁶ Previous transplant experience had suggested that non-identical, T cell depleted grafts, could be as successful as HLA-identical procedures in LAD, but our survey has found a high levels of primary graft failure, which resulted in secondary (or tertiary) grafting in all 8 haploidentical transplants. Consequently, only 4/8 (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 following either matched family donor or unrelated donor transplantation was notably better. Thus 12/14 (86%) recipients of unrelated donor HSCT survived, and this was comparable to 11/14 (79%) of the matched family donor recipients.

Nine patients (4 haploidentical, 3 sibling donor and 2 matched unrelated donor) did not survive following transplantation (Table 2). All had received myeloablative conditioning and donor engraftment was established in seven patients, albeit after repeat procedures in five cases. Infection related deaths occurred in 5 cases, with 3 deaths linked to veno-occlusive disease and one case of secondary malignancy (EBV lymphoma). We noted that six deaths occurred in the first seven-year period of this analysis (1993-2000) compared to three deaths in the subsequent period (2001-2007). This probably reflects the reduced use of haploidentical donors in the second period, rather than any generalised improvements in transplantation procedures or supportive care in recent years.

Complications that may be anticipated following allogeneic stem cell transplantation include GVHD, infections and the toxic side effects of chemotherapy. Nine patients developed GVHD at grade II or greater, including two cases of severe grade IV skin and gut GVHD (one MFD and the other a 1-antigen mismatched MUD). Viral reactivations of CMV, EBV, Adenovirus and Varicella Zoster were detected, and there were at least two significant cases of unexplained pneumonitis. Veno-occlusive disease in three cases followed Busulphan based conditioning, and contributed to the cause of death in these cases. Overall the use of RIC regimens appeared to be associated with reduced toxicity, with all 8 patients in this subgroup surviving, although two (patients no 2 and 22) have low level donor chimerism. With twenty seven surviving patients followed-up for a median of 62 months, full chimerism has been recorded in 17, 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 has very low levels of chimerism in both lineages (~5%) but remains symptom-free. The remaining three patients have lymphoid engraftment (one full, two mixed) but no documented engraftment of donor granulocytes, and these patients also remain well but continue to receive close monitoring.

DISCUSSION

We report the transplant experience for LAD for procedures undertaken at 14 centres 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 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 the previous experience of successful haploidentical transplantation in LAD had 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 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 donors¹⁰⁻¹⁴ 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 pre-existing organ dysfunction, a number of these procedures were performed using modified, reduced intensity regimens. We have previously documented improved survival 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 pre-conditioning in these patients will be of particular interest considering that intact fertility and uncomplicated pregnancies have been reported in dogs with canine LAD (CLAD) following non-myeloablative SCT.¹⁶

Interestingly, low levels of donor neutrophil engraftment as measured in peripheral blood appear 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 a 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, leucocytes can prevent disease.²¹ Transplant studies in CLAD have indicated that less than 500 CD18⁺ donor neutrophils/microL 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 to 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 haematopoietic stem cells transduced to express canine CD18 corrected 5-10% 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. Further investigation of these patients may be warranted, including detailed lineage specific chimaerism in tissues (in the bone marrow and gingival tissues) and the exclusion of host mediated cellular or autoantibody responses against donor derived cells.

CONCLUSION

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 appears 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.

Acknowledgments

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Abbreviations

ARA-C	Cytarabine
ARDS	Acute respiratory distress syndrome
ATG	Antithymocyte globulin
BM	Bone Marrow
Bu	Busulphan
Cam1G	Campath 1G
Cam1H	Campath 1H
CLAD	Canine leukocyte adhesion deficiency
CMV	Cytomegalovirus
CY	Cyclophosphamide
CyA	Cyclosporin
EBV	Epstein Barr Virus
FISH	fluorescent <i>in situ</i> hybridization
GVHD	Graft versus host disease
HAPL	Haloidentical donor (P-paternal, M-maternal)
HSCT	Haematopoietic stem cell transplantation
LAD	Leukocyte adhesion deficiency
MFD	Matched family donor
MMUD	Mismatched unrelated donor
MSD	Matched sibling donor
MUD	Matched unrelated donor
PBSC	Peripheral blood stem cell collection
MNC	mononuclear cells
Mtx	Methotrexate
MMF	Mycophenolate mofetil
PMN	Polymorphonuclear cells
Prd	prednisolone
RIC	reduced intensity conditioning
T dep	T cell depleted
TP	Thiopeta
UCB	Umbilical cord blood
VP16	Etoposide

VOD	Veno-occlusive disease
VZV	Varicella zoster virus

Table 1

Patients surviving after allogeneic transplantation for LAD

Donor	Age mths	Year BMT	Follow-up (mths)	Conditioning	Graft	Prophyl-axis	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	BM	CyA MMF	II	CMV	MNC 30
3 MFD	3	2007	5	*Flu Treo Cam1H	BM	CyA MMF			Full
4 MSD	78	1994	156	Bu VP16	UCB			Pneumonit is	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	BM	CyA		CMV, EBV	PMN100 MNC92
15 MUD	24	2001	72	*Flu Mel Cam1H	BM	CyA	II/III	ADV	Full
16 MUD	36	2001	74	*Flu Mel Cam1H	BM	CyA		Crypto	PMN 87 MNC 93
17 MUD	24	2003	62	*Flu Mel Cam1H	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	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	UCB	CyA Prdd			PMN 3 MNC 5
23 MUD 3AMM	7	1997	93	Bu CY ATG	UCB	CyA Prd	I	Candida	Full
24	i. HAPL	7	1999	i. Bu CY TP	UCB	CyA Prd	I		Full
	ii. HAPL			ii. Flu Mel ATG					
25	i. HAPL(P)	2	2000	i. Bu CY ATG					Full
	ii. HAPL(M)			ii. Flu aCD3					
	iii. HAPL(M)			iii. None					

Donor	Age mths	Year BMT	Follow-up (mths)	Conditioning	Graft	Prophyl-axis	Gvhd	Infections	Chimerism
26	i. HAPL	2003	48	i. Bu CY ATG	i. PBSC/CD34	III			Full
	ii. HAPL			ii. Flu Mel TP Cam1G	ii. PBSC/CD34				
27	i. HAPL	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				

Table 2

Patients not surviving after allogeneic transplantation for LAD

Donor	Age (months)	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 Pred		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 αLFA-1 αCD2	i. BM T dep			Yes	Infection VOD
ii. HAPL(M)			ii. BU CY VP16 Cam1G	ii. BM T dep				
8 i. HAPL(P)	3	1997	i. BU CY αCD2	i. BM T dep	CyA		Yes	Infection
ii. HAPL(M)			ii. BU CY αCD2 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				

* Indicates Reduced Intensity Conditioning (RIC). Other abbreviations for Tables 1 & 2: ARA-C, Cycarabine; ARDS, Acute respiratory distress syndrome; ATG, Antithymocyte globulin; BM, Bone Marrow; Bu, Busulphan; Cam1G, Campath 1G; Cam1H, Campath 1H; CMV, Cytomegalovirus; CY Cyclophosphamide; CyA, Cyclosporin; EBV, Epstein Barr Virus; HAPL, Haplodentical donor (P-paternal, M-maternal); MFD, Matched family donor; MSD, Matched sibling donor; MUD, Matched unrelated donor; MMUD, Mismatched unrelated donor (1-3 antigens); PBSC, Peripheral blood stem cell collection (CD34 selected where indicated); MNC, mononuclear cells; Mtx, Methotrexate; MMF, Mycophenolate mofetil; PMN, Polymorphonuclear cells; Prd, prednisolone; T dep, T cell depleted; TP, Thiopeta; UCB, Umbilical cord blood; VP16, Etoposide; VOD, Veno-occlusive disease; VZV, Varicella zoster virus