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Allogeneic Hematopoietic Stem Cell Transplantation in Leukocyte Adhesion Deficiency Type 1: A Single Center Experience

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Leukocyte adhesion deficiency type 1 is a rare autosomal recessive immunodeficiency disorder. The severe phenotype is fatal unless hematopoietic stem cell transplantation (HSCT) is performed. A retrospective analysis was performed in 11 patients with leukocyte adhesion deficiency type 1 who underwent HSCT and monitoring over a period of 19 years at our institution. The median age at HSCT was 8.8 months. Stem cell sources were unmanipulated bone marrow from an HLA-matched related donor in 7 patients, unrelated umbilical cord blood in 3 patients, and a mismatched related donor in 1 patient. Three patients underwent a second HSCT. Conditioning was provided with a busulfan- and cyclophosphamide-based regimen, with anti-thymocyte immunoglobulin added for the cord blood transplant recipients. Graft-versus-host-disease prophylaxis consisted of cyclosporine A and methotrexate for related donor recipients (8 patients) and cyclosporine A and prednisone for cord blood transplant recipients (3 patients). The overall event-free survival rate was 91% with a median follow-up of 94 months (range, 15-223 months). Ten patients had immune reconstitution and demonstrated sustained engraftment that ranged from 11% to 100% for lymphoid lines and from 0% to 100% for myeloid lines. HSCT from a matched related donor or unrelated cord blood provided excellent outcome, and mixed chimerism appeared satisfactory to prevent recurrent infections.

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INTRODUCTION

Leukocyte adhesion deficiency type 1 (LAD-1) is a rare autosomal recessive immunodeficiency disorder caused by defects in the common β2 subunit (CD18) of the leukocyte integrins imposed by various types of mutations [1-3]. The aberrant β2 integrin is either undetectable or is unable to properly associate with the α subunits. In severe deficiency, cell surface expression of the β2 integrin heterodimers is <1% of normal levels. These patients usually develop recurrent infections of the skin and lungs, systemic sepsis, delayed umbilical cord separation, omphalitis, impaired pus formation, and delayed wound healing associated with leukocytosis [4-5]. Patients often die within the first year secondary to infection.

Allogeneic hematopoietic stem cell transplantation (HSCT) offers the possibility of cure for patents with LAD-1 [6-8]. However, because LAD-1 is extremely rare, experience in any particular center is limited. A previous 2-center study reported the outcome of 14 matched related and haploidentical donor transplants performed between 1982 and 1993, with a survival rate of 71% at 12 months to 12 years post-HSCT [9]. These studies addressed particular difficulties associated with HSCT for LAD-1, mainly graft rejection and graft-versus-host-disease (GVHD).

Data from the registries of the European Society for Immunodeficiencies, European Group for Blood and Marrow Transplantation, and Center for

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International Blood and Marrow Transplant Research show an overall survival rate of 75% in 36 children with LAD-1 who underwent HSCT [10]. Outcomes were comparable in matched related donor (MRD) and unrelated donor HSCTs. Although the number of successful unrelated umbilical cord blood (UR-CB) HSCTs for LAD-1 is limited, UR-CB appears to be a promising option in the absence of an MRD [11].

Here, we describe the outcome of one of the largest single-center study of patients with LAD-1 who underwent HSCT from an MRD, UR-CB, or a mismatched related donor (MMRD).

PATIENTS AND METHODS

Patients

Eleven patients with severe LAD-1 underwent HSCT at King Faisal Specialist Hospital and Research Center in Riyadh between January 1991 and December 2008. The diagnosis of LAD-1 was confirmed by flow cytometric analysis demonstrating defective expression of <1% CD11/CD18 on the surface of lymphocytes and granulocytes. This retrospective chart review with multivariable factors was approved by the Research Advisory Council at King Faisal Specialist Hospital and Research Center. Data obtained included the patients' pre-HSCT clinical and immunologic characteristics, HSCT characteristics, and post-HSCT complications (ie, age at HSCT, donor characteristics, HLA matching, conditioning regimen, stem cell origin, $CD34^+$ cell dose, bone marrow manipulation, engraftment, GVHD, infections, toxicity, and outcome), and immune reconstitution post-HSCT at last follow-up. Isolated pathogens were evaluated by culture or polymerase chain reaction of the material obtained by specimen collection or biopsy.

Conditioning Regimen

The conditioning regimen consisted of busulfan (BU) 1 mg/kg/dose orally every 6 hours for 4 days (total dose, 16 mg/kg) on days -10 to -7 and cyclophosphamide (CY) 50 mg/kg/dose i.v. for 4 days (total dose, 200 mg/kg) on days -5 to -2. Rabbit anti-thymocyte immunoglobulin (rATG) at 10 mg/kg/dose i.v. for 4 days (total dose, 40 mg/kg) on days -5 to -2 was added for UR-CB recipients.

Three patients (2, 5, and 9) required a second HSCT. The conditioning regimen consisted of BU and CY for patient 2, and VP-16 (etoposide) at 300 mg/m^2/dose × 3 doses (900 mg/m^2) i.v. on days -5 to -2 and rATG with a total dose of 40 mg/kg in addition to BU and CY for patient 5. In contrast, patient 9 received total-body irradiation (TBI) in addition to CY and rATG. Patient 2 underwent T cell depletion with alemtuzumab (Campath).

The grafts were unmanipulated marrow from HLA-genoidentical siblings in 7 patients, UR-CB in 3 patients, and mismatched sibling (2-antigen mismatch at the HLA-DR and -DQ loci) for 1 patient. A serologic technique was used for HLA class 1 (-A, -B, and -C loci), and a molecular technique was used for HLA class 2 (-DRB1 and -DQB1 loci).

GVHD Prophylaxis

GVHD prophylaxis consisted of cyclosporine A (CsA) and methotrexate (MTX) at standard doses for patients undergoing MRD and MMRD HSCT, and CsA and methylprednisolone for patients undergoing UR-CB HSCT. CsA was tapered in the absence of GVHD after 100 days in the MRD recipients and after 180 days in UR-CB recipients.

Supportive Care

All patients were placed in a high-efficiency particulate air–filtered rooms until their absolute neutrophil count exceeded 0.5×10^9/L for 3 consecutive days. Intravenous immunoglobulin was administered every 2 weeks at a dose of 0.5 g/kg starting on day -7 before HSCT and continuing until B cell recovery was achieved. All blood products were irradiated and leukocyte-filtered. All patients received acyclovir prophylaxis for 28 days starting on day -3 before HSCT. Bone marrow recovery was defined as an absolute neutrophil count $>0.5 \times 10^9$/L and an unsupported platelet count $>20 \times 10^9$/L for 3 consecutive days.

Engraftment and GVHD

Chimerism was analyzed by fluorescence in situ hybridization in sex-mismatched donors and by variable number tandem repeat in same-sex donors. In 2004, both of these techniques were supplanted by the short tandem repeat technique. Immune reconstitution was demonstrated by flow cytometric detection of CD11/CD18 expression on lymphocyte and granulocyte surfaces.

GVHD (acute and chronic) was defined according to standard criteria and confirmed by histopathologic diagnosis when necessary [12,13]. All patients were treated with the standard protocol and received additional immunomodulatory therapy as needed.

RESULTS

Pretransplantation Status

Fourteen HSCTs were performed in 11 patients with the severe LAD-1 phenotype. Nine patients were diagnosed based on typical clinical presentation and lack of CD18 expression on neutrophils and monocytes (<1%); the other 2 patients were diagnosed through newborn screening based on a positive family

Table 1. Clinical Characteristics of Patients Pre-HSCT

Patient	Sex	Age at Diagnosis, Months	Clinical Presentation	Organisms Isolated
1	F	13	Delayed cord separation; secretory otitis media; skin and mucous membrane ulcers/sepsis	*Pseudomonas*/*Staphylococcus* spp; *Streptococcus viridans*
2	F	1.5	Skin infection and ulcers; omphilitis	
3	M	16	Pneumonia; secretory otitis media; skin infection; sepsis	*Candida*/*Staphylococcus* spp; *Klebsiella pneumoniae*; *Escherichia coli*/*Enterobacter aerogenes*; Group D enterococci; *Streptococcus viridans*
4	F	9	Perianal skin infection; omphilitis	*Staphylococcus* spp; *Pseudomonas*
5	M	0.25	Delayed cord separation; skin infection; perianal abscess; pneumonia; secretory otitis media	Group D enterococci; *Pseudomonas*/*Candida*; *Staphylococcus* spp
6	F	0.25	Delayed cord separation; skin infection	*Staphylococcus* spp/*Pseudomonas*; *Enterococcus faecalis*; *Klebsiella pneumoniae*
7	M	2	Omphilitis; pneumonia; skin infection	*Staphylococcus* spp; methicillin-resistant *Staphylococcus aureus*
8	F	2	Omphilitis; respiratory syncytial virus pneumonia	*Staphylococcus* spp
9	M	1	Pneumonia	
10	F	1	Skin infection; omphilitis	
11	F	4	Pneumonia; delayed cord separation	

history. The median age at diagnosis was 4.7 months (range, 1-16 months). Pretransplantation clinical characteristics are summarized in Table 1.

The graft sources were an MRD in 7 patients, UR-CB in 3 patients, and an MMRD in 1 patient. Three patients (2, 5, and 9) required a second HSCT. Patients 2 and 5 underwent the second HSCT with a graft from the same donor as for their first HSCT, whereas patient 9 did so with a different UR-CB source. The median age at HSCT was 8.8 months (range, 3-18 months). The median $CD34^+$ stem cell–infused dose was 8.9×10^6/kg (range, 4.93-13.97 $\times 10^6$/kg) in related HSCT and 0.28×10^6/kg (range, 0.04-0.56 $\times 10^6$/kg) in UR-CB HSCT (Table 2). The median total nucleated cell count was 0.76×10^9/kg (range, 0.41-1.33 $\times 10^9$/kg).

Engraftment and Immune Reconstitution

The median time to neutrophil recovery was 19 days (range, 13-36 days), and that to platelet recovery was 34 days (range, 14-56 days). Seven patients engrafted after their first HSCT and maintained stable immune reconstitution. Patient 7 had stable donor lymphoid cell engraftment as detected by chimerism study and CD18 expression. He continued to demonstrate low CD18 expression (1%) on granulocytes despite undetectable myeloid cell engraftment.

As shown in Table 2, 3 patients (2, 5, and 9) required a second HSCT because of engraftment failure (27% failure rate). After the second HSCT, successful engraftment was achieved in patients 5 and 9. Overall, 9 out of the 11 patients demonstrated stable immune reconstitution, for a success rate of 82%.

On last follow-up, post-HSCT chimerism analysis found a median chimerism of 70% (range, 11%-100%) for lymphocytes and 55% (range, 0%-100%) for myeloid cells. Post-HSCT median CD18 expression over granulocytes and lymphocytes was 58% (range, 1%-100%) and 61% (range, 18%-93%), respectively,

Table 2. BMT Characteristics

Patient	Age at HSCT, Months	Donor	CD34/kg, $\times 10^6$	Conditioning Regimen	GVHD Prophylaxis	Complications/GVHD	T Cell Depletion
1	17	Matched sibling	9.26	BU/CY	CsA/MTX		-
2	7	Haploidentical brother		BU/CY	CsA/MTX		-
	9	Haploidentical brother		BU/CY	CsA/MTX	Sepsis	+
3	18	Matched sibling	13.97	BU/CY	CsA/MTX		-
4	11	Matched sibling	8.39	BU/CY	CsA/MTX		-
5	3	Matched sibling	5.13	BU/CY	CsA/MTX		-
	9	Matched sibling	12.14	BU/CY/VP16/ATG	CsA/MTX	Mastoidectomy with hearing loss	-
6	7	Matched sibling	4.93	BU/CY	CsA/MTX	Acute grade II skin GVHD	-
7	8	UR-CB	0.56	BU/CY/ATG	CsA/methylprednisolone	Pneumonia, sepsis	-
8	3	UR-CB	0.19	BU/CY/ATG	CsA/methylprednisolone	Pneumonia, mucositis	-
9	6	UR-CB	0.04	BU/CY/ATG	CsA/methylprednisolone	AIHA, AIT	-
	14	UR-CB	0.34	CY/ATG/TBI	CsA/methylprednisolone		-
10	5	Matched sibling	9.26	BU/CY	CsA/MTX	Mucositis, VOD	-
11	6	Matched sibling	8.25	BU/CY	CsA/MTX	VOD	

AIHA indicates autoimmune hemolytic anemia; AIT, autoimmune thrombocytopenia; VOD, veno-occlusive disease.

Table 3. Immune Reconstitution at the Last Follow-Up

		CD18		FISH/STR		
Patient	Months Post-HSCT	Granulocytes	Lymphocytes	Myeloid	Lymphoid	Survival
1	223	35	64	ND	ND	A/W
2	—	—	—	—	—	Died
3	161	60	18	ND	ND	A/W
4	157	63	90	71	81	A/W
5	140	39	74	43	53	A/W
6	122	99	39	ND	ND	A/W
7	37	1	18	0	11	A/W
8	35	85	89	100	85	A/W
9	19	100	93	100	100	A/W
10	22	3	36	7	62	A/W
11	15	90	89	63	100	A/W

FISH indicates fluorescence in situ hybridization; STR, single tandem repeat; A/W, alive and well; ND, not done.

with a median follow-up of 94 months (range, 15-223 months), as shown in Table 3.

GVHD

Acute grade II skin GVHD occurred in 1 patient (patient 6), who responded well to treatment with steroids and CsA. None of the patients developed chronic GVHD.

Survival and Complications

Event-free survival was 91% for all patients, with 100% (6/6) for MRD recipients and 100% (3/3) for UR-CB recipients. One patient (patient 2) died after the second HSCT secondary to bacterial sepsis. Suspected veno-occlusive disease occurred in two patients (patients 10 and 11), whereas autoimmune hemolytic anemia and autoimmune thrombocytopenia occurred in only one patient (patient 9). No patient developed viral disease or reactivation.

DISCUSSION

LAD-1 is a rare immunodeficiency disorder worldwide; however, it seems to be more common in the Arabian Peninsula, including Saudi Arabia. As has been demonstrated in other types of primary immunodeficiencies [14-16], this higher prevalence is likely related to the high incidence of consanguinity in Saudi Arabia, which approaches 50% [17].

This retrospective analysis of 14 HSCTs performed in 11 patients with LAD-1 is one of the largest case series reported from a single center to date. It clearly demonstrates that HSCT can provide a cure for LAD-1, as has been reported previously [6-10]. Moreover, we found a 100% event-free survival and 90% stable immune reconstitution for MRD and UR-CB HSCT recipients, with minimal toxicity.

The post-HSCT level of functional CD18 expression necessary to prevent infection has not been well explored; however, observations from animal studies suggest that low levels can prevent recurrent infection [18,19]. Thomas et al. [9] reported that levels of mixed engraftment as low as 5% may be sufficient to prevent major infections. In agreement with this, 2 of our patients (7 and 10) had a CD18 expression level of 1%-3%, which seemed sufficient to prevent major infections (Figures 1 and 2). Interestingly, patient 7 continued to express very low CD18 expression on granulocytes despite no detectable donor myeloid cells. This indicates that close monitoring and follow-up for such asymptomatic patients is a plausible approach to determining the need for a second HSCT.

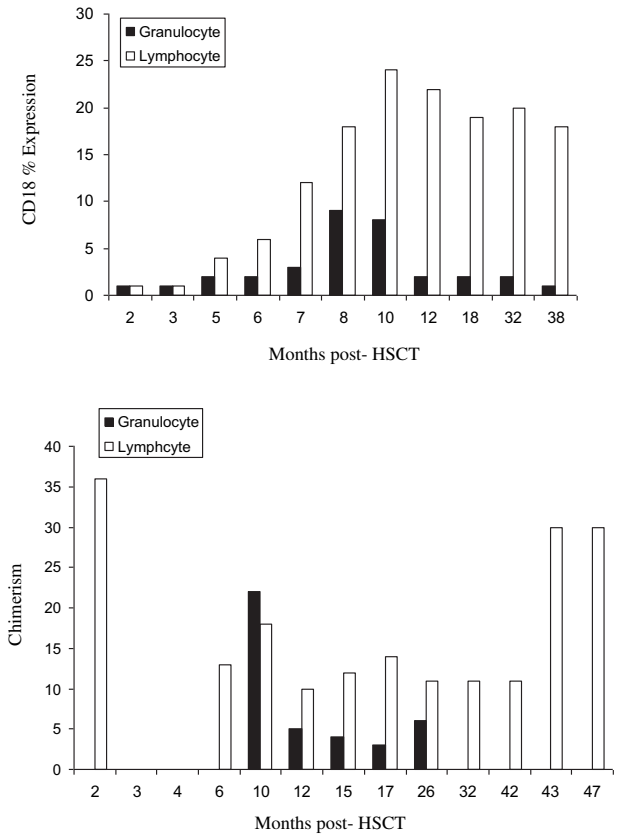

Figure 1. Patient 7, CD18 expression and chimerism.

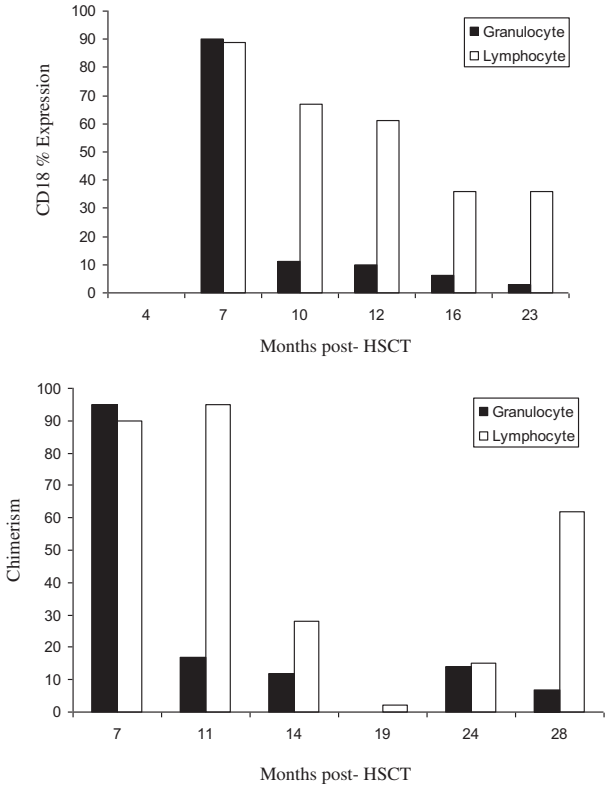

Figure 2. Patient 10, CD18 expression and chimerism.

Although there are limited data on the use of UR-CB HSCT in LAD-1, our study and others suggest that UR-CB is a promising alternative when a fully matched donor is not available [10,11]. Three patients (7, 8, and 9) received 4 UR-CB transplants at ages 3, 6, 8, and 15 months. Two of these patients successfully engrafted with full donor cell chimerism, even though one of them (patient 9) achieved this only after the second HSCT. The overall event-free survival was 100%. The conditioning regimen was well tolerated, with neither toxicity nor GVHD complications seen.

Our results demonstrate a low incidence of GVHD, likely related to the availability of fully matched siblings in our cohort. Long-term follow-up in all patients found a survival rate of 91% with a median follow-up of 9 years. Three patients (5, 7, and 10) remained asymptomatic with low CD18 expression. Further large, multicenter studies on the long-term outcome of HSCT in LAD-1 are needed.

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