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Nonmyeloablative Stem Cell Transplantation with Alemtuzumab/Low-Dose Irradiation to Cure and Improve the Quality of Life of Adults with Sickle Cell Disease

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) is rarely performed in adult patients with sickle cell disease (SCD). We utilized the chemotherapy-free, alemtuzumab/total body irradiation 300 cGy regimen with sirolimus as post-transplantation immunosuppression in 13 high-risk SCD adult patients between November 2011 and June 2014. Patients received matched related donor (MRD) granulocyte colony–stimulating factor–mobilized peripheral blood stem cells, including 2 cases that were ABO incompatible. Quality-of-life (QoL) measurements were performed at different time points after HSCT. All 13 patients initially engrafted. A stable mixed donor/recipient chimerism was maintained in 12 patients (92%), whereas 1 patient not compliant with sirolimus experienced secondary graft failure. With a median follow-up of 22 months (range, 12 to 44 months) there was no mortality, no acute or chronic graft-versus-host disease (GVHD), and no grades 3 or 4 extramedullary toxicities. At 1 year after transplantation, patients with stable donor chimerism have normalized hemoglobin concentrations and improved cardiopulmonary and QoL parameters including bodily pain, general health, and vitality. In 4 patients, sirolimus was stopped without rejection or SCD-related complications. These results underscore the successful use of a chemotherapy-free regimen in MRD HSCT for high-risk adult SCD patients and demonstrates a high cure rate, absence of GVHD or mortality, and improvement in QoL including the applicability of this regimen in ABO mismatched cases (NCT number 01499888).

INTRODUCTION

Sickle cell disease (SCD) is often characterized by acute and chronic complications that progress with increasing age and negatively impact the patients' quality of life (QoL), lead to chronic morbidity, and result in high utilization of health care resources and reduced survival [1-3]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option currently available for patients with SCD [4-7]. Previously, few studies had addressed the role of allogeneic HSCT in adult SCD patients, particularly those over 30 years of age [8]. In contrast, pediatric studies have shown encouraging results with HSCT using myeloablative [4-7]

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or reduced doses of chemotherapy in the conditioning regimen [9,10]. More recently, 2 studies have shown that nonmyeloablative regimens result in engraftment of HLA-matched related grafts in a high proportion of adult SCD patients without significant morbidity [11,12]. In the current study, we independently validate the unique experience of a chemotherapy-free allogeneic HSCT developed at the National Institutes of Health (NIH). We are the first to demonstrate the feasibility of this innovative regimen in ABO-mismatched recipients and report on its impact on QoL in adult SCD patients.

METHODS

Study Design and Eligibility

The primary endpoint of this prospective, phase I/II study (NCT number 01499888) was the engraftment rate at 1 year after HSCT. Secondary endpoints included transplantation-related toxicity, acute and chronic graft-versus-host disease (GVHD), SCD-related complications, QoL, and overall and disease-free survival. The protocol was approved by the University of Illinois at Chicago's institutional review board and written informed consent was obtained for all patients and donors in accordance with the Declaration of Helsinki.

Patients between the ages of 16 and 60 years with a diagnosis of SCD (genotypes Hb SS, Hb SC, Hb Sβ0-thalassemia, or Hb Sβ+-thalassemia) and complicated by 1 of the following were considered eligible for the study: (1) stroke, (2) ≥3 vaso-occlusive crises (VOC) per year requiring medical attention, (3) ≥2 life-time episodes of acute chest syndrome, (4) ≥2 episodes of priapism per year requiring medical attention, (5) red blood cell (RBC) alloimmunization during chronic transfusion therapy, (6) bilateral proliferative retinopathy with major visual impairment in at least 1 eye, (7) ≥2 joints with avascular necrosis, (8) chronic kidney disease, (9) stage I or II chronic lung disease, or (10) pulmonary hypertension defined as symptoms consistent with pulmonary hypertension and mean pulmonary artery pressure >25 mmHg. Additional eligibility requirements included having an HLA-identical matched related donor (MRD), being competent to sign informed consent, and having a Karnofsky score > 70, estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2, left ventricular ejection fraction > 40%, and diffusing capacity of the lung for carbon monoxide > 50% predicted. Active hepatitis and a diagnosis of cirrhosis were exclusion criteria. The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) was calculated from baseline data before HSCT as previously described [13].

Donors

Related donors were matched to the patients at the HLA-A, -B, -C, -DR, and -DQ loci by low-resolution molecular typing. Individuals with sickle cell trait were not excluded as donors. Donors received granulocyte colony–stimulating factor subcutaneously at a dose of 10 μg/kg/day to 12 μg/kg/day for 5 days followed by peripheral blood stem cell collection.

Transplantation Regimen

Patients underwent an RBC exchange transfusion using RBCs that were leukoreduced, irradiated, and matched for Rh, Kell, Kidd, Duffy, and MNS blood group antigens at day −10 with the goal of Hb S < 30%. Hydroxyurea was permanently discontinued at day −8 before stem cell infusion. Alemtuzumab (anti-CD52 monoclonal antibody) was administered intravenously as follows: .03 mg/kg on day −7, .1 mg/kg on day −6, and .3 mg/kg/day on days −5 to −3. Total body irradiation (TBI) was given as a single dose of 300 cGy on day −2. Immunosuppressive therapy with oral sirolimus was started on day −1. In addition to standard antimicrobial prophylaxis, patients received penicillin V potassium (250 mg twice daily) until pneumococcal vaccination was completed. Platelet transfusions were given for platelet counts $<50 \times 10^9$ cells/L. Standard engraftment criteria for neutrophils and platelets were followed and donor cell chimerism was measured in the whole blood and in circulating $CD3^+$ selected cells on days +30, +60, +90, +180, +365 and annually thereafter. Transthoracic echocardiograms and pulmonary function testing were performed before HSCT and 1 year after HSCT. Patients with T cell chimerism > 50% at day +365 were considered for sirolimus withdrawal.

QoL

Health-related QoL (HRQoL) was measured using short form (SF-36) v1 [14] at 4 time-points: before HSCT and at days +30, +90, and +365 after HSCT. Based on the patients' responses to the 36 items, scores were calculated for each of the 8 domains and normalized to the values of the United States' population (mean, 50; SD, 10) [15]. The SF-6D, which provides an overall utility score based on societal weights derived for items on the SF-36, was also calculated [16].

Statistical Analysis

Clinical and laboratory data are reported as median values (range). Continuous variables were compared using the paired *t*-test when appropriate using Systat 11 (Systat Software Corporation, San Jose, CA). Descriptive statistics were calculated for all HRQoL scores across different visits. HRQoL analyses were performed using repeated-measures ANOVA or the paired *t*-test. Standardized response means (SRM) were calculated at each visit as a measure of effect size and to evaluate the magnitude of change over time [17]. SRM was calculated as the ratio of the mean change score and the variability (standard deviation) of the change score for the group. Cohen's thresholds (.2 = small, .5 = medium, and .8 = large) were used to interpret the SRM scores [18]. Analysis of HRQoL data was restricted to patients who had completed the 1-year post-HSCT assessment.

RESULTS

Patient Characteristics

Between November 2011 and June 2014, 61 patients with SCD were referred for evaluation and 13 patients (Hb SS = 12, Hb SC = 1) between the ages of 17 and 40 years underwent allogeneic HSCT. Reasons for exclusion included lack of a suitable donor (n = 29), insurance denial (n = 11), or the patient declining further evaluation (n = 8). The characteristics of the 13 patients who underwent transplantation, including the indications for HSCT and the HCT-CI score, are shown in Table 1. Eight of the 13 patients were on hydroxyurea therapy for a minimum of 3 years before initiating the conditioning regimen. Twelve of the 13 patients had multiple SCD-related complications that met eligibility requirements. Four of the patients had RBC alloimmunization (median number of antibodies, 4; range, 2 to 7) and 2 patient-donor pairs were mismatched for the major ABO blood types (patient number 8: recipient A+, donor B+; patient number 13: recipient O+, donor A+). Granulocyte colony–stimulating factor–mobilized peripheral blood stem cells were collected from all 13 donors, including 4 with sickle cell trait, without complication. The median dose of $CD34^+$ cells transplanted was 8.2×10^6 $CD34^+$ cells/kg (range, 5.1 to 15.3×10^6 $CD34^+$ cells/kg).

Engraftment

Of the 13 patients, 11 had severe neutropenia ($<.5 \times 10^9$ neutrophils/dL) for a median duration of 6 days (range, 2 to 18 days) (Figure 1). Three patients had a platelet count that decreased to $<50 \times 10^9$ cells/L requiring platelet transfusions and 10 patients required RBC transfusions (median number of RBC units transfused, 1; range, 0 to 4) to maintain a hemoglobin between 9 g/dL and 10 g/dL. The median length of hospitalization was 33 days (range, 13 to 51 days). Donor cell chimerism at different time points is shown in Figure 2 and did not differ in patients who maintained a low (5 ng/mL to 10 ng/mL) versus high (10 ng/mL to 15 ng/mL) therapeutic serum level of sirolimus (data not shown). One patient who was noncompliant with sirolimus developed secondary loss of engraftment by day +90. At 1 year after HSCT, 12 of the 13 patients (92%) maintained stable donor chimerism (median whole blood chimerism, 81%; range, 31% to 98%; median $CD3^+$ chimerism, 43%; range, 10% to 86%) (Figure 2).

Transplantation-related Toxicity

Conditioning with alemtuzumab and low-dose TBI was generally well tolerated and no transplantation-related mortality was observed. Extramedullary toxicities > grade

Table 1
Patient and Donor Characteristics of 13 Patients with Sickle Cell Disease Receiving an Allogeneic HSCT from an HLA-Matched Sibling

Recipient							Donor			
No.	Age at Transplantation, yr	Gender	Hemoglobin Genotype	Indications	Prior Therapy	HCT-CI Score	Gender	Hemoglobin Genotype	ABO Compatibility	$CD34^+$ Dose, 10^6/kg
1	33	F	SS	12 VOC/year, AVN of multiple joints	HU	3	F	AA	Matched	7.7
2	24	M	SS	5 VOC/year, AVN of multiple joints, CKD, priapisms	HU	4	M	AA	Matched	11.1
3	19	M	SS	Multiple episodes of acute chest syndrome, 4 VOC/year	HU	6	M	AA	Matched	10.5
4	25	M	SS	6 VOC/year, priapism	HU	6	M	AS	Matched	8.1
5	40	M	SC	5 VOC/year, bilateral retinopathy, AVN of multiple joints, priapism	HU	0	M	AA	Matched	9.6
6	27	F	SS	Stroke, RBC alloimmunization on chronic transfusion therapy	Chronic transfusion	5	F	AA	Matched	6.5
7	35	F	SS	4 VOC/year, multiple episodes of acute chest syndrome, AVN of multiple joints	HU	3	M	AA	Matched	15.3
8	33	F	SS	7 VOC/year, multiple episodes of acute chest syndrome	HU	1	M	AS	ABO Mismatch	5.1
9	32	F	SS	Stroke, 12 VOC/year, pulmonary hypertension, AVN of multiple joints	Chronic transfusion	3	F	AS	Matched	8.1
10	38	M	SS	4 VOC/year, multiple episodes of acute chest syndrome, AVN of multiple joints	HU	5	F	AA	Matched	10.0
11	19	M	SS	Stroke, multiple episodes of acute chest syndrome	Chronic transfusion	4	M	AS	Matched	4.9
12	17	M	SS	12 VOC/year	None	3	F	AA	Matched	4.1
13	30	F	SS	Stroke, multiple episodes of acute chest syndrome, CKD	Chronic transfusion	0	F	AA	ABO mismatch	5.9

ABO indicates ABO blood group; F, female; SS, homozygous hemoglobin S disease; AVN, avascular necrosis; HU, hydroxyurea; AA, homozygous hemoglobin A; M, male; CKD, chronic kidney disease; AS, sickle cell trait; SC, compound heterozygous hemoglobin S and C disease.

I observed in the study are shown in Table 2. Of the 3 patients who had cytomegalovirus reactivation (as detected by quantitative DNA monitoring in the blood), all were successfully treated with preemptive valgancyclovir and none developed cytomegalovirus disease. Six patients had arthralgias attributed to the sirolimus therapy, with 2 patients requiring dose reductions. One patient developed chest pain and a decline in carbon monoxide diffusion capacity by 30%, which was attributed to sirolimus. Sirolimus was discontinued and replaced by cyclosporine on day +105. This patient developed posterior reversible encephalopathy syndrome on day +126 and the cyclosporine was changed to mycophenolate mofetil on day +131. This patient has since maintained stable donor chimerism with improvement in the carbon monoxide diffusing capacity close to the patient's baseline value.

Transplantation Outcome

In the 12 patients with stable engraftment, hemoglobin fractionations are consistent with the donor's hemoglobin type (Figure 3A). Hemoglobin values improved from median baseline values of 7.8 g/dL (range, 6.6 g/dL to 8.4 g/dL) in women and 8.1 g/dL (range, 7.6 g/dL to 12.4 g/dL) in men to 12.4 g/dL (range, 10.9 g/dL to 13.1 g/dL) in women and 15.0 g/dL (range, 10.8 g/dL to 16.8 g/dL) in men at 1 year after HSCT ($P < .0001$) (Figure 3B). Similarly, there were significant declines in the reticulocyte percentage from 11.5% (range, 4.8% to 19.6%) to 1.9% (range, 1.4% to 5.8%) ($P = .001$), lactate dehydrogenase concentration from 326 u/L (range, 208 u/L to 663 u/L) to 211 u/L (range, 161 u/L to 382 u/L) ($P = .038$), and a trend towards a decrease in the indirect bilirubin concentration from 1.5 mg/dL (range, .3 mg/dL to 20.9 mg/dL) to .9 mg/dL (range, .4 mg/dL to 1.8 mg/dL) ($P = .10$) between baseline values before HSCT and 1 year after HSCT, respectively. After HSCT, there was only 1 engrafted patient who required readmission to the hospital for VOC and this occurred in a patient who had 12 VOC per year before HSCT. No other SCD-related complications occurred in the 12 patients with stable donor chimerism. Cardiac (brain-natriuretic peptide [BNP] level and left atrial diameter) and pulmonary function improvements were recorded at 1 year and are shown in Figure 4. Both patients with major ABO mismatches had stable engraftment and have not required RBC transfusions or developed SCD-related complications after engraftment.

At a median follow up of 22 months (range, 12 to 44 months), all 13 patients are alive with a disease-free survival rate of 92% (12 of 13 patients with stable donor chimerism). No patients have developed acute or chronic GVHD and 4 patients have been successfully titrated off sirolimus after HSCT.

Improved QoL after HSCT

Of the 12 engrafted subjects with 1 year of follow-up, 9 completed the SF-36 assessments at both the pre-HSCT and 1-year post-HSCT time points. The results (Figure 5A) show that at 1 year after HSCT, with the exception of physical functioning, the mean scores of the patients in all SF-36 domains were within one half a standard deviation (SD) of the population mean scores (mean = 50 ± 10). Across multiple visits, a significant effect was observed for general health (F [3, 30] = 4.03; $P = .016$), vitality (F [3, 30] = 2.99; $P = .047$), social functioning (F [3, 30] = 3.31; $P = .033$), and the overall preference-based summary score (SF-6D) (F [3, 26] = 4.60; $P = .01$). At the 1-year post-HSCT assessment, marked improvements in the bodily pain, general

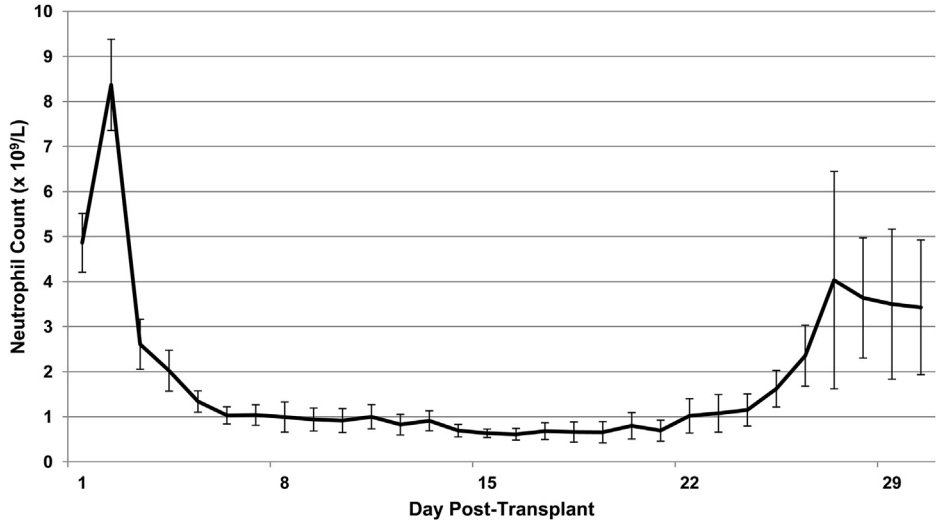

Figure 1. Neutropenia after alemtuzumab/TBI conditioning in adult SCD patients. Neutrophil counts after conditioning with alemtuzumab/total body irradiation and hematopoietic stem cell transplantation. Each value represents the mean neutrophil count ± standard error (n = 13).

health, and vitality domains were observed, along with lesser effects on the social functioning and mental health domains. The improvement in estimated SF-6D index scores between each successive time point exceeded the commonly accepted minimally important difference of .033 (Figure 5B) [19].

DISCUSSION

Our study demonstrates that a nonmyeloablative and chemotherapy-free, HLA-matched related HSCT conditioned with alemtuzumab and low-dose TBI can normalize the hemoglobin concentration in 92% of adult patients with clinically aggressive SCD, reduce SCD-related complications, and significantly improve cardiopulmonary function and QoL without transplantation-related mortality. These results validate the success of this innovative regimen, previously reported from a single institution [11,20]. Our study is also the first to show that this type of transplantation can be successfully used in the setting of major ABO incompatibility between the donor and recipient and results in objective and significantly progressive improvements in the QoL of adult SCD patients starting at day +30 to day +365 after HSCT.

Of more than 450 allogeneic HSCT that have been reported to treat patients with clinically aggressive SCD, more than 90% were performed in children or young adults <30 years of age. Myeloablative regimens in children have resulted in engraftment rates of 86% to 97%, transplantation-related mortality rates of 3% to 7%, acute GVHD (grade II or greater) rates of 10% to 20%, and chronic GVHD rates of 13% to 22% [4,5,7]. In the pediatric setting, increasing age appeared to be a risk factor for GVHD [4] and, in a cohort of 15 young adult SCD patients who underwent a myeloablative regimen, acute GVHD ≥ grade II occurred in 8 patients (53%), chronic GVHD in 2 patients (13%), and transplantation-related death in 1 patient (7%) [21]. In contrast to these findings, 2 nonmyeloablative conditioning regimens have recently demonstrated success with low toxicity in adult SCD patients. A regimen using fludarabine/low-dose cyclophosphamide followed by high-dose cyclophosphamide on days +3 and +4 after HSCT demonstrated long-term engraftment in 3 of 3 HLA-matched related HSCT, although there may be a risk for

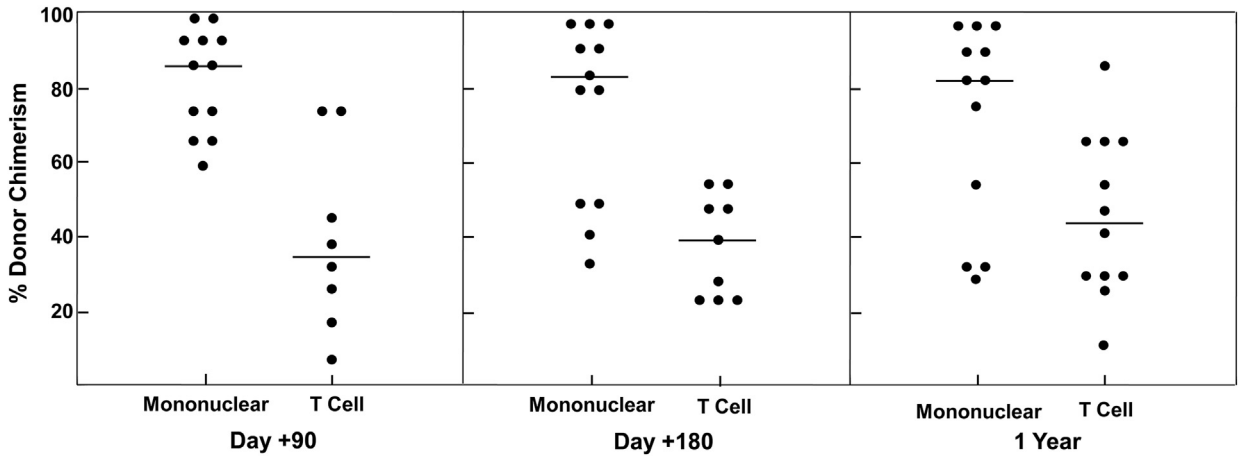

Figure 2. Engraftment analysis after alemtuzumab/TBI conditioning in adult SCD patients. Whole blood mononuclear cell (MNC) and $CD3^+$ lymphoid cell chimerism values at day +90, day +180, and day +365 after hematopoietic stem cell transplantation (HSCT) in the 12 patients with stable engraftment.

Table 2
Transplantation-Related Toxicity

Patient No.	Transplantation-Related Toxicity	Living Status	Length of Follow-Up, mo	Duration of ANC < 500, d	Platelet Units Transfused	RBC Units Transfused	CMV Reactivation
1	Day +100: GNR in hip prosthesis	Alive	44	0	0	3	None
2	None	Alive	38	2	0	1	None
3	Day −5: DHTR after exchange transfusion	Alive	34	3	0	0	None
4	Day +94: Viral pharyngitis	Alive	33	4	0	0	None
5	None	Alive	26	4	0	0	None
6	Day +3: Grade II mucositis	Alive	23	7	0	1	None
7	Day +70: MRSA pneumonia	Alive	21	14	0	2	Day +18
8	Day +2: Grade II mucositis Day +4: Line-associated DVT	Alive	20	8	1	3	Day +39
9	Day +1: ESBL UTI Day +20: *C. difficile* colitis Day +28: *M. pneumoniae*	Alive	17	0	0	3	None
10	None	Alive	17	5	0	1	None
11	Day +167: *Coxsackie B*	Alive	17	2	0	1	None
12	None	Alive	15	14	1	4	Day +12
13	None	Alive	12	16	1	3	None

ANC indicates absolute neutrophil count; CMV, cytomegalovirus; GNR, gram-negative rods; DHTR, delayed hemolytic transfusion reaction; MRSA, methicillin-resistant *Staphylococcus aureus*; DVT, deep vein thrombosis; ESBL, extended spectrum beta-lactamase; UTI, urinary tract infection.

GVHD and none of these patients were off immunosuppression at the time of the report [12]. Another regimen developed at the NIH using alemtuzumab/low-dose TBI followed by post-transplantation immunosuppressive monotherapy with sirolimus reported a success rate of 87% with very low morbidity in 30 patients [11,20].

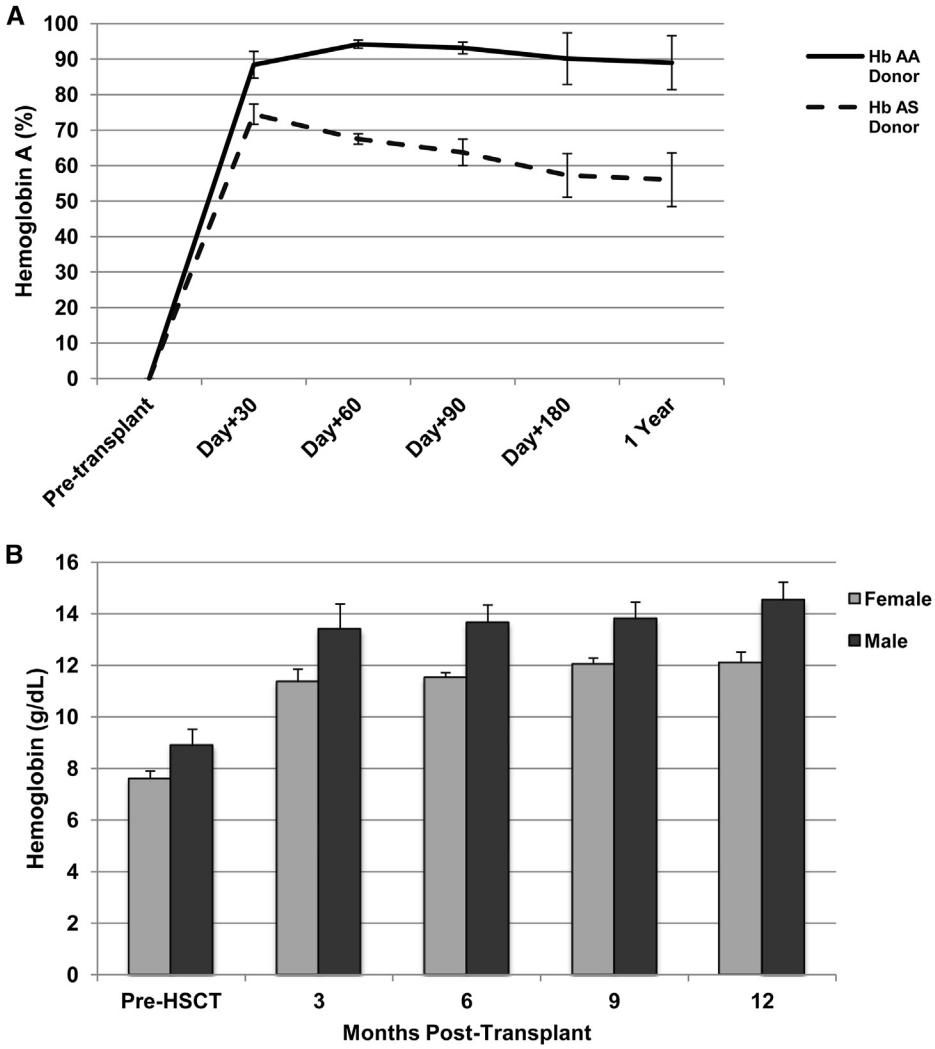

Figure 3. Normalization of hemoglobin after alemtuzumab/TBI conditioning in adult SCD patients. Hemoglobin fractionation studies and total hemoglobin concentrations after hematopoietic stem cell transplantation in 12 patients with stable engraftment. (A) The proportion of hemoglobin A in the recipients was stable and consistent with the proportion observed in the donor. (B) Mean hemoglobin concentrations ± standard errors by sex of recipient.

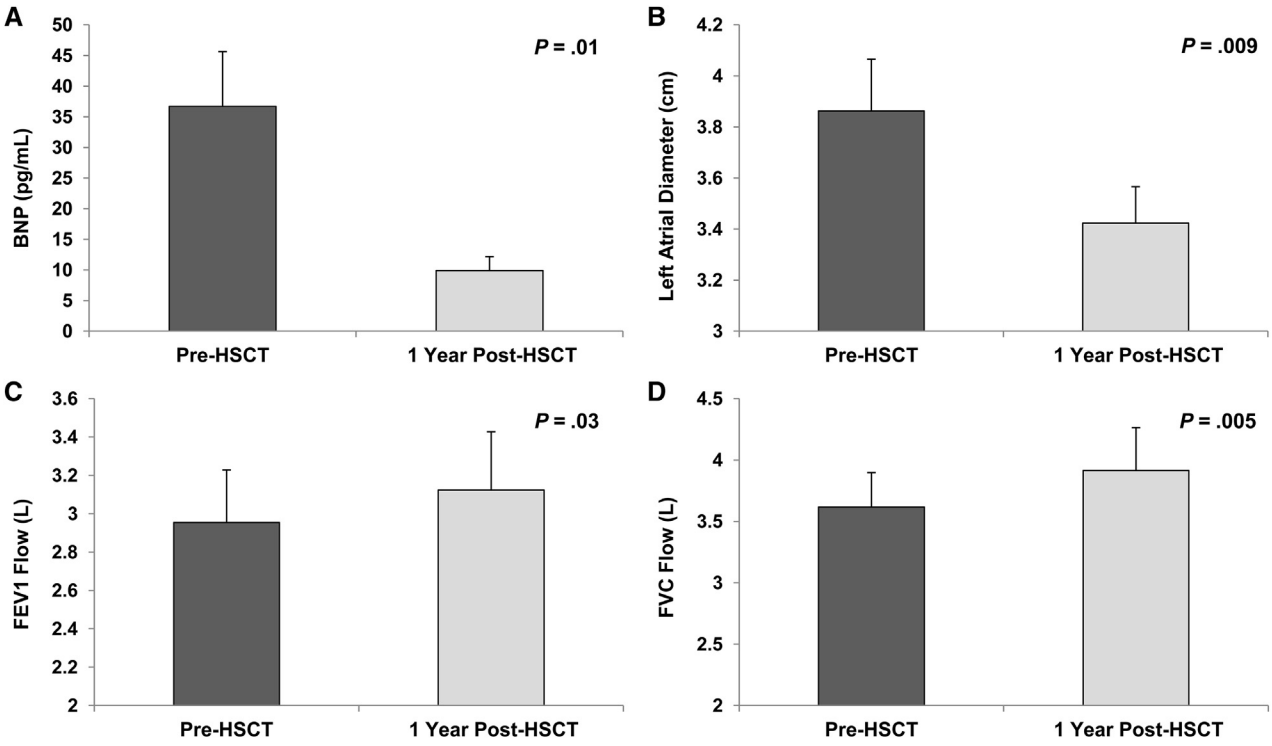

Figure 4. Cardiopulmonary improvement after alemtuzumab/TBI conditioning in adult SCD patients. Cardiopulmonary improvement at 1 year post-hematopoietic stem cell transplantation was observed in 12 patients with stable engraftment. (A) Brain-natriuretic peptide (BNP) concentrations, (B) Left atrial diameter, (C) Forced expiratory volume at 1 second (FEV1), and (D) Forced vital capacity (FVC) measurements are given as mean values ± standard error.

We used this latter approach in our center with the aims of validating the NIH study as well as addressing the pressing needs of a large cohort of adult SCD patients at our center who have high utilization of health care resources from VOC and other acute and chronic SCD-related complications, poor QoL, and reduced survival rates.

Before initiating this study, we identified some major challenges unique to SCD patients undergoing HSCT, including the following: (1) the majority of high-risk SCD patients have an HCT-CI score ≥ 3, which is usually associated with an increased risk of nonrelapse mortality after HSCT [13]; and (2) the care of SCD in an urban setting is often affected by limitations in social support and transportation difficulties for a highly demanding condition that could affect post-HSCT management. One of our 13 patients decided to interrupt the immunosuppressive therapy at 30 days after HSCT without following up in clinic and experienced full rejection with recovery of SCD. In the remaining 12 patients, we observed improvement of the hemoglobin concentrations with almost complete absence of SCD-related complications. In addition, 4 patients were able to discontinue immunosuppression with sirolimus at 1 year and remain in complete clinical and hematologic remission. Our findings show that even low levels of donor cell chimerism are sufficient to prevent relapse of SCD, consistent with previous studies [22,23]. However, the immunologic mechanism by which a donor to host T cell chimerism unbalanced in favor of the latter permits a predominant (and at times, complete) stable donor erythropoiesis in such patients is unknown.

This study independently validates the previous findings from the NIH, showing that a chemotherapy-free conditioning regimen based on immunosuppressive therapy alone allows engraftment of MRD peripheral blood stem cells without transplantation-related mortality, acute GVHD, or chronic GVHD. Unlike the NIH study, we included ABO mismatched donors in 2 cases where no other MRD were available. Both patients engrafted donor stem cells successfully without major signs of hemolysis or anemia after the transplantation. Another difference was that our patients were maintained on immunosuppression with sirolimus targeting a trough serum level of 5 ng/mL to 15 ng/mL, as compared to the targeted trough level of 10 ng/mL to 15 ng/mL in the NIH cohort [11,20]. This may be clinically relevant, as the transplantation-related toxicities observed in our study, primarily oral mucositis (grade I, grade II in 2 cases) and 1 case of noninfectious pneumonitis, were likely related to sirolimus as the symptoms improved upon holding the medication or reducing the dose. Confirmation of our finding that a lower trough level of sirolimus results in chimerism levels equivalent to those observed at a higher level should help reduce the arthralgias, mucositis, and pulmonary toxicities associated with this medication [24]. Finally, we performed a progressive assessment of our patients' HRQoL; previously examined in pediatric but not in adult SCD patients undergoing HSCT. A brief reduction in HRQoL in the initial period after HSCT has been previously observed in pediatric patients (predominantly undergoing a myeloablative conditioning regimen) [25], followed by significant improvements in physical, emotional, and overall health measurements at 1 year after HSCT in 2 cohorts [25,26]. However, a third pediatric SCD cohort was unable to show a significant difference in HRQoL scores between SCD patients who had undergone HSCT versus SCD patients who did not undergo HSCT [27]. Using a nonmyeloablative conditioning regimen in adult SCD patients, we demonstrate an improvement in HRQoL as early as at day +30 after HSCT,

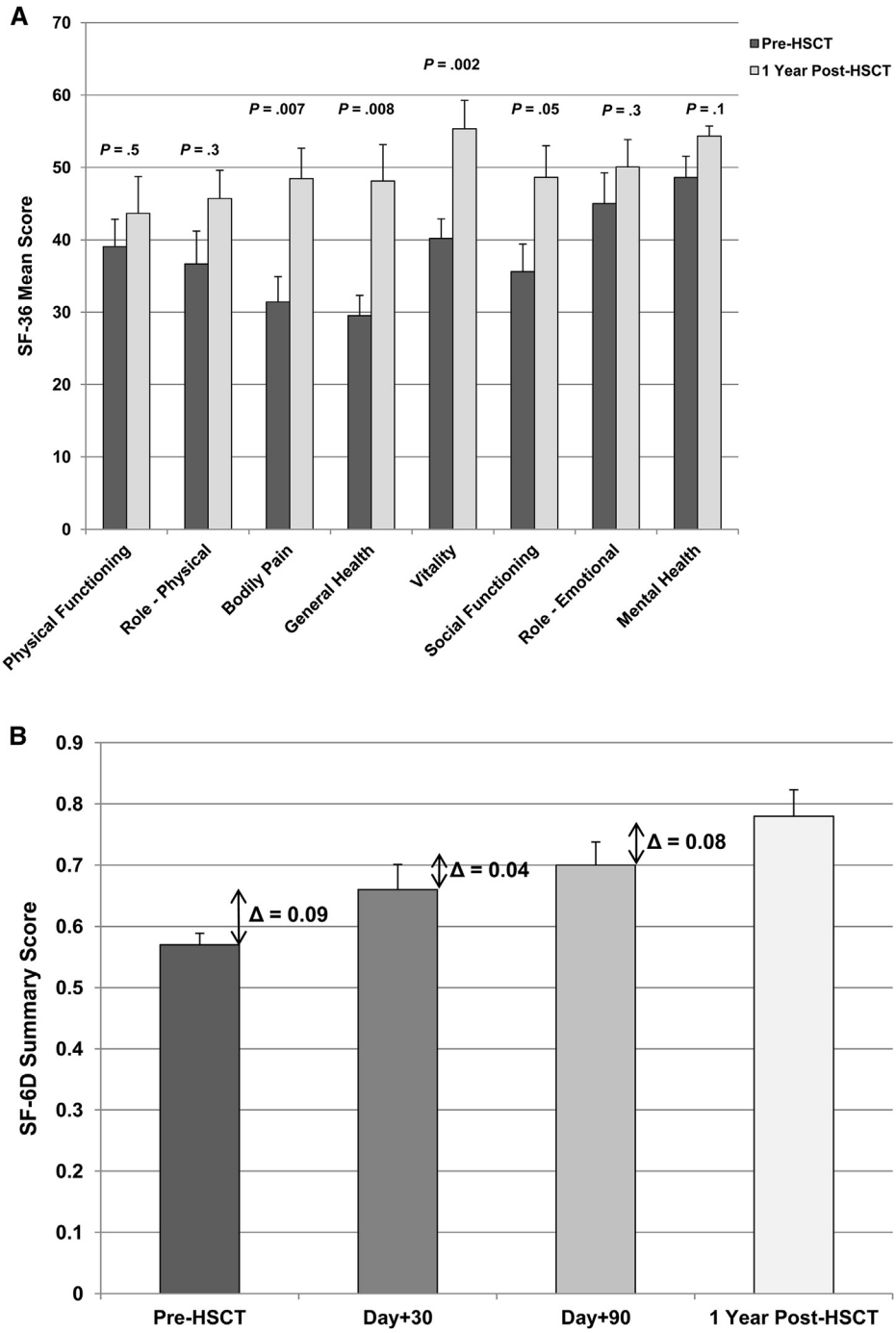

Figure 5. Rapid and sustained improvement in the HRQoL after HSCT in adult SCD patients. Improvements in normalized HRQoL scores and SF-6D scores between before and after HSCT in 9 patients with stable engraftment. (A) SF-36 mean scores ± standard error across the eight HRQoL domains. Differences between pre- and post-HRQoL scores were analyzed and *P* values are shown. (B) SF-6D mean scores ± standard error at each time point of assessment. $\Delta > .033$ represents the commonly accepted minimally important difference.

along with significantly greater improvements in general health, bodily pain, and vitality at 1 year after HSCT. This is the first series of adult SCD patients with documented improvements in QoL after undergoing an allogeneic HSCT. The cumulative data from our center and the NIH should provide a strong incentive for other centers, where high-risk SCD patients are currently followed, to consider this innovative therapy. In addition, because of the low toxicity and risk of GVHD, it may be conceivable that this type of HSCT from MRD could be implemented in economically challenged areas of the world with high prevalences of SCD, such as in some areas of India or Africa [28].

The lack of suitable HLA-matched donors prevents many SCD patients from receiving HSCT, a potentially curative therapy. It is estimated that less than 20% of SCD patients who meet eligibility criteria will have a suitable HLA-matched donor [29,30]. The novel approach of using haploidentical donors through the combination of a reduced-intensity conditioning regimen before HSCT followed by high-dose cyclophosphamide on day +3 and +4

after HSCT may help to overcome this barrier, although the risk of graft failure remains higher than in MRD HSCT [12]. Alemtuzumab may not be commonly available and studies using antithymocyte globulin, which should not affect regulatory T cell number or function, should be considered [31]. More studies utilizing nonmyeloablative conditioning regimens in allogeneic HSCT for SCD are warranted to establish standard-of-care procedures to cure adult SCD patients. This will have a significant impact on patients who are otherwise condemned to live with progressive complications and worsening QoL, and, in some cases, are still being denied insurance coverage for HSCT because of a lack of data and the historically high rates of complications and death.

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