Prevalence and Reversibility of Pulmonary Dysfunction in Refractory Systemic Lupus*

Improvement Correlates With Disease Remission Following Hematopoietic Stem Cell Transplantation

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Aim: **To report the prevalence and reversibility of pulmonary function test (PFT) abnormalities among systemic lupus erythematosus (SLE) patients, refractory to therapy, undergoing hematopoietic stem cell transplantation (HSCT).**

Methods: **Thirty-four SLE patients received 200 mg/kg cyclophosphamide and 90 mg/kg equine antithymocyte globulin followed by HSCT. PFTs were performed prior to, at 6 months, and yearly following HSCT.**

Results: **The prevalence of significant PFT abnormalities was high (97%). Low FEV_1 and FVC occurred in 26 of 34 patients (76%). A significant abnormality in diffusion capacity of the lung for carbon monoxide (DLCO) occurred in 26 of 32 individuals able to complete DLCO testing (81%). DLCO ≤ 50% of predicted occurred in 18 of 32 patients (56%). Of these 18 patients, 4 had no thoracic diagnosis and 7 had no pulmonary diagnosis. For 3 of 11 patients with a DLCO ≤ 50% of predicted and a prior pulmonary diagnosis, the only diagnosis had been pleurisy. Ten of the 34 patients (29%) identified the lung as a target organ of the lupus and carried a pulmonary diagnosis, as indicated in Table 1. Three patients had acute alveolar hemorrhage, four patients had acute lupus pneumonitis, two patients had shrinking lung syndrome (SLS), and one patient had SLE-related pulmonary hypertension. Of these 10 patients, 4 had received prior mechanical ventilation, and 7 had required home supplemental inspired oxygen. Patients have been monitored ≤ 77 months, and 28 patients have been monitored > 18 months after HSCT. Five of 28 patients had a normal entry FVC; for each, the FVC remains normal. Of the 23 patients with an abnormal baseline FVC, 18 have improved, 15 completely and 3 partially. Eight of these 18 patients also have improved DLCO. The two patients with a diagnosis of SLS and one patient with SLE-related pulmonary hypertension improved in both parameters. Only 5 of 23 patients with an abnormal FVC did not improve. Each of these five patients retained active lupus in spite of HSCT.**

Conclusion: **The prevalence of lung impairment among SLE patients requiring long-term immune suppression is high. Following HSCT, pulmonary impairments can improve, which is sustained if disease control is sustained.** ***(CHEST 2005; 127:1680–1689)***

Key words: acute interstitial pneumonitis; alveolar hemorrhage; cyclophosphamide; hematopoietic stem-cell transplant; systemic lupus erythematosus

Abbreviations: AAH = acute alveolar hemorrhage; ALP = acute lupus pneumonitis; APLS = antiphospholipid syndrome; ATG = antithymocyte globulin; BCNU = bischloroethylnitrosourea; BILAG = British Isles Lupus Assessment Group; DLCO = diffusion capacity of the lung for carbon monoxide; HSCT = hematopoietic stem-cell transplantation; MVR = mitral valve regurgitation; PE = pulmonary embolus; PFT = pulmonary function test; SLE = systemic lupus erythematosus; SLS = shrinking lung syndrome; TLC = total lung capacity

Deficiencies in pulmonary function have been estimated to occur in up to 80% of unselected patients with systemic lupus erythematosus (SLE), often in the presence of normal chest radiographic findings.[1–3] Pleuropulmonary manifestations described in lupus include diaphragmatic dysfunction, pleural effusion, acute lupus pneumonitis (ALP), pulmonary hemorrhage, pulmonary hypertension, diffuse interstitial lung disease, syndrome of acute reversible hypoxemia and, rarely, bronchiolitis obliterans with organizing pneumonia. This topic was recently well reviewed by Keane and Lynch.[4]

Pulmonary function is routinely monitored prospectively in autologous bone marrow transplant recipients, because a decline in pulmonary function, both acute and chronic, is well described following

autologous bone marrow transplantation.[5–15] Long-term follow-up of pediatric patients undergoing transplantation has shown that a restrictive pattern commonly develops after receipt of the more aggressive preparative regimens, those typically utilized for leukemia in relapse or lymphoma (*ie*, cyclophosphamide, total body irradiation, and bischloroethylnitrosourea [BCNU], or cyclophosphamide, etoposide, and BCNU).[10,14,15] A restrictive pattern rarely occurs following the milder preparative regimens, which are used for children with leukemia in first remission or with aplastic anemia.[14]

The risk of pulmonary toxicity from high-dose cyclophosphamide, when used as a single agent, is not well established. Multidrug regimens, which include high doses of ifosphamide or cyclophosphamide, administered in conjunction with another chemotherapeutic agent or radiation, have been associated with pulmonary toxicity.[6,7] However, the other agents most commonly used with cyclophosphamide include high-dose BCNU and high-dose busulfan, both inherently toxic to the lung. When cyclophosphamide is used with antithymocyte globulin (ATG), as it was here and is in the preparative regimen for aplastic anemia, pulmonary toxicity has not been a problem. Children receiving transplantation for aplastic anemia have not shown a decline in pulmonary function as they have with more aggressive combination chemotherapy or radiation regimens.[14] Therefore, we anticipated that individuals would not show a decline in pulmonary function following the cyclophosphamide and ATG preparative regimen. Here we report changes in pulmonary function following hematopoietic stem-cell transplantation (HSCT), and correlate improvement in pulmonary function with improvement in disease activity, defined by the British Isles Lupus Assessment Group (BILAG) scale.[16] We fully anticipated that pulmonary function test (PFT) results would improve in the subset of patients who underwent HSCT for lung disease, if they achieved sustained remission from active SLE. We underestimated the prevalence of severe lung disease in this population, and likewise underestimated the significant rate of improvement in lung function with HSCT for SLE in all patients. We were impressed by the manner in which abnormalities of lung function could track SLE activity.

The rationale for anticipating improvement in SLE-affected organ systems with the HSCT approach, after conventional therapeutic approaches have been insufficient, is that escalation of therapy, by eliminating larger proportions of B- and T-lymphocyte populations, may eliminate a more substantial population of disease-mediating memory cells.[17] Timely infusion of hematopoeitc stem cells may then allow a reestablishment of immune diversity without aberrant skewing. Symptoms and serologic evidence of SLE tend to disappear gradually over 6 months following HSCT.[17,18] Another theorized contribution toward improvement in pulmonary function may be the successful tapering of systemic corticosteroids if disease remission is obtained.[18] Successful corticosteroid taper may improve diaphragm force generation and improve body habitus, thereby increasing FVC. An absence of pleuritic chest pain may also contribute to improved pulmonary function in selected patients.

Materials and Methods

Whenever possible and in the majority of instances, PFTs were performed for all time points in the Pulmonary Function Laboratory at Northwestern Memorial Hospital in Chicago, and echocardiography was performed with Doppler interrogation in the Echocardiography Suite at Northwestern Memorial Hospital. For spirometry and diffusion capacity of the lung for carbon monoxide (DLCO) measurements, the equipment used was a V6200 Autobox or 22c system (SensorMedics; Yorba Linda, CA), which utilizes mass flow sensor technology to measure flows and volumes, using the Burrow norms for calculation. The V6200 Autobox uses mass flow sensor technology during plethysmography. The 22c uses mass flow sensor technology during nitrogen washout. In rare instances, follow-up studies were obtained off-site at the patient's insistence. Due to the severely ill nature of some patients at presentation, some suboptimal echocardiogram windows were obtained.

For the purpose of this analysis, values of FEV_1, FVC, or total lung capacity (TLC) $< 80\%$ of the predicted value were considered significantly below normal. DLCO, adjusted for hemoglobin DLCO, $< 70\%$ of the predicted value for the patient was considered significantly low. All results listed for DLCO were corrected for hemoglobin concentration. A restrictive defect was defined as a low ($< 80\%$ predicted) value for both FVC and TLC. An obstructive defect was defined by decreased FEV_1 and a decreased FEV_1/FVC. Bronchodilator was not administered. Obstructive defects were not seen.

HSCT was performed after obtaining Food and Drug Administration- and Investigational Review Board-approved informed consent. Pretreatment screening included an evaluation of pulmonary and cardiac function, as well as full medical history, physical examination, and laboratory measures of lupus activity. All patients then received a "mobilization" (pre-stem cell harvest) dosage of cyclophosphamide (2 g/m^2) in order to synchronize the

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Table 1—*Characteristics of Transplant Recipients at Study Entry**

SLE Patient No./Age, yr	Thoracic Diagnosis	FEV_1, % Predicted	FVC, % Predicted	TLC, % Predicted	DLCO, % Predicted	DLCO Adjusted for Volume Averaging, % Predicted	Prednisone Dosage per Day, mg	Major Indication for HSCT	Prior Mechanical Ventilation/ Supplemental Oxygen Use
1/24	MVR	52	60	67	49	86	40	ARF, HTN	No/yes
2/25	AAH/ALP BAL/ by biopsy	78	74	107	42	88	30	AAH	Yes/yes
3/26	SLS	31	50	67	Unable to complete	Unable to complete	30	Hypoxia, musculoskeletal pain	No/yes
4/17	Pleurisy	75	77	Not done	93	60	40	Cerebritis, CRF	No/yes
5/39	ALP by biopsy	75	76	76	41	62	20	Hypoxia, MS pain	No/yes
6/16	Pleurisy	37	42	54	42	80	20	Cerebritis, glomerulonephritis	No/no
7/51	None	80	81	68	81	116	18	MS pain	No/no
8/20	None	51	52	69	63	94	18	Mucocutaneous vasculitis	No/no
9/28	None	79	75	89	61	94	28	Glomerulonephritis, musculoskeletal pain	No/no
10/16	AAH by BAL	79	86	80	42	76	10	AAH, cerebritis	Yes/no
11/27	Thoracic myelitis	36	31	Not done	23	55	20	Myelitis	Yes/no
12/50	SLS	46	50	64	54	141	20	Hypoxia	No/yes
13/18	None	62	67	94	67	62	30	Cerebritis	No/no
14/28	None	159	154	170	127	114	20	Cerebritis, musculoskeletal pain	No/no
15/22	None	77	72	71	83	110	30	Cerebritis, thrombocytopenia	No/no
16/38	Pulmonary vasculitis	64	61	59	26	65	20	Cutaneous vasculitis	No/yes
17/20	History of PE, pleurisy	40	36	44	41	143	20	Cerebritis, musculoskeletal pain	No/yes
18/45	Pleurisy	62	48	67	54	94	20	Cerebritis, neuropathy	No/no
19/32	None	72	69	68	57	80	30	AIHA, cerebritis	No/no
20/22	Pleurisy	41	38	36	34	107	40	Cerebritis, musculoskeletal pain	No/no
21/29	None	64	66	73	45	86	30	Cerebritis	No/no
22/22	Pleurisy, severe MVR	85	79	85	44	57	20	Myocarditis, musculoskeletal pain	No/no
23/48	ALP	48	56	99	Unable to complete	Unable to complete	None at time of testing	Cerebritis, musculoskeletal pain	No/no
24/21	Pulmonary hypertension	68	72	74	48	70	12	Calciphylaxis	No/no
25/52	None	95	97	86	72	91	25	Cerebritis	No/no
26/34	None	59	60	70	40	66	30	Cerebritis neuropathy	No/no
27/37	APLS, history of PE	91	88	95	78	91	20	CVA, APLS	No/no
28/36	None	77	75	65	39	47	7.5	Cerebritis, MS pain	No/no
29/40	None	95	89	95	58	70	12	Cerebritis, MS pain	No/no
30/24	Thoracic myositis	56	53	55	50	98	12	Myositis, muscuoskeletal pain	No/no
31/36	Pleurisy	52	55	66	39	70	30	Cutaneous vasculitis, calcinosis, cerebritis	No/no
32/27	AAH	66	66	78	42	73	12	AAH and nephritis	Yes/yes
33/32	History of PE	76	75	77	54	74	5	Nephritis, musculoskeletal pain	No/no
34/27	None	86	81	79	45	70	20	Cutaneous vasculitis	No/no

*ARF = acute renal failure; HTN = hypertension; CRF = chronic renal failure; MS = musculoskeletal; CVA = cerebrovascular accident.

circulation of a high number of circulating hematopoietic stem cells into the peripheral blood stream approximately 10 days later. This recovery was followed by collection and lymphocyte depletion of hematopoietic stem cells by CD34-positive selection (Isolex cell separator; Baxtor; Deerfield, IL). The following week, a transplant conditioning regimen consisting of 200 mg/kg cyclophosphamide divided over 4 days and 90 mg/kg ATG divided over 3 days was administered; this was followed 36 h later by infusion of CD34-selected hematopoietic stem cells. At the time of study entry, the daily prednisone dosage varied from 20 to 60 mg/d, which was maintained during transplantation. All other immune suppressive therapies were discontinued. After HSCT, the prednisone dosage was tapered by 5 to 10% monthly for the first 6 months and 10 to 20% per month during the second 6 months, with a goal of < 10 mg/d prednisone by 12 months. Supportive care included prophylactic monthly, aerosolized pentamidine, 300 mg by inhalation nebulizer every 4 weeks, and valacyclovir, 400 mg po bid for 1 year, along with oral fluconazole, 400 mg/d, until completion of steroid taper. During periods of neutropenia, patients empirically received either pipercillin/sulbactam or cefepime IV and daily IV liposomal amphotericin.

The BILAG test is a validated clinical instrument used to measure lupus disease activity in all organ systems.[16] The BILAG has developed a scoring system to evaluate the current disease activity and the changes in disease activity from the last assessment. The evaluation is based on a five-category classification characterizing the degree of symptoms attributed to active lupus from 86 questions based on the patient's history, examination, and laboratory results.[16] The 86 questions are grouped into eight systems: general, mucocutaneous, neurologic, musculoskeletal, cardiovascular and respiratory, vasculitic, renal, and hematologic. For each of the eight systems, a severity grade (A-E) is calculated based on the scores. Grade A disease is active enough to need treatment. Grade B disease has the potential to need treatment soon. Grade C disease currently does not meet grade A or B criteria. Grade D disease has satisfactorily resolved, and grade E disease has never occurred in this system. By definition, all patients entering this trial were in BILAG grade A.

Statistical Analysis

Since FVC and DLCO were measured for each patient at multiple time points, to test for statistically significant changes in FVC and DLCO over time, a mixed-effect general linear model for repeated measurements was applied.[19] Disease activity (with/without SLE disease remission) after HSCT, as well as age, were controlled in the model. Descriptive statistics, medians in FVC and DLCO at each time point, were calculated and plotted to show their changes over time. In this study, a clinically significant improvement is defined as a 12% increase in predicted FVC or DLCO. A Fisher exact test was used for comparing the proportion of clinically significant improvement in FVC and DLCO between patients with and without persistent SLE activity. Analysis was done using statistical software (SAS version 8.2; SAS Institute; Cary, NC).[19]

RESULTS

Pulmonary Outcome

Baseline PFT results of each of the 34 HSCT patients are listed in Table 1 with any preexisting lung or cardiac diagnoses. Also listed in Table 1 are the patient age at study entry, prednisone dose at study entry, the major SLE-affected organ system necessitating the HSCT, and two elements of pulmonary history: whether the patient had previously required mechanical ventilation and whether the patient was receiving long-term supplemental oxygen. Thirteen patients had no history of cardiopulmonary disease prior to HSCT. As stated above, 10 patients had a long-term diagnosis of the lung itself, including acute alveolar hemorrhage (AAH) or ALP (7 patients), shrinking lung syndrome (SLS) [2 patients], and pulmonary hypertension (1 patient). In addition to these 10 patients, there were 3 patients with a prior history of pulmonary embolus (PE), one in the setting of antiphospholipid syndrome (APLS). Eight patients had a history of pleurisy. There were also established, nonpulmonary diagnoses that impacted lung function. Two of the patients had moderate or severe mitral valve regurgitation (MVR). One patient had myelitis and one patient had myositis, which involved the thoracic spinal cord and/or musculature. All patients with prior echocardiograms are listed in Table 2.

A decrease in DLCO, adjusted for hemoglobin, was the most common abnormality detected during the baseline screening, occurring in 26 of 32 patients who were able to complete the DLCO measurement (81%). Including inability to complete the diffusion measurement with optimal supervision as an abnormality of DLCO, 28 of 34 patients (82%) had an abnormal DLCO. Low FEV_1 and low FVC occurred in 27 patients and 27 patients, respectively, of the total 34 patients (79%). TLC was decreased in 23 of 34 patients (68%). A low FVC and low TLC occurred in 22 of 32 patients for whom both measurements were performed (69%). Pulmonary function abnormalities occurred commonly in the absence of overt respiratory symptoms. Of the 15 patients with no prior cardiac history or pulmonary diagnosis, no history of PE and no history of pleurisy, 14 had at least one abnormality of pulmonary function detected.

There was no transplant-related mortality. Patients received an average of 3.2×10^6 CD34 cells per kilogram, and engraftment averaged day 8. One year following HSCT, all patients were alive and free of supplemental oxygen use. Changes in FVC following HSCT are plotted for individual patients in Figure 1. Among the 28 patients with available data extending over 12 months, 8 patients experienced persistent SLE activity that required therapy (BILAG grade A). Twenty patients did not. Among the eight patients with persistent disease activity evident by 6 to 23 months after HSCT, FVC was unchanged (changed $< 12\%$ of predicted value) in seven individuals (86%) or improved in one individual (14%) at 12 months following HSCT. In contrast, of the 20 individuals who remained without active SLE, FVC

Table 2—*Doppler Echocardiographic and Systolic Function Results in 13 Transplant Recipients**

SLE Patient No.	Findings
1	Concentric LVH; LV myocardium has ground-glass appearance; moderate pericardial effusion; electrical alternans; diastolic indentation of RA; MV leaflets myxomatous with normal opening; normal LVEF; mild MR; mild TR; estimated PA systolic pressure, 40 mm Hg
2	Thickened MV; LV shortening fraction 28%; heart rate, 120 beats/min; moderate MR; mild TR; unable to estimate RV pressure
3	LV systolic function normal, normal flow across the MV and AV; no TR
9	Fractional shortening 55%; valves normal: trace MR and TR with normal estimated PA pressure; concentric LVH
11	Normal LV structure and function; thickened MV
12	Grossly normal LVEF; normal MV; E:A reversal consistent with decreased LV compliance; minimal TR; estimated RVSP, 37 mm Hg; high-resolution CT unremarkable
13	LVEF normal; MV and TV motion normal; no MR or TR
17	Hyperdynamic LV function; forward flow across the MV is normal; no MR; mild TR; cannot estimate RV pressure
20	Normal ventricular size; LVEF normal; forward flow normal across all valves; no MR or AI; mild TR and mild pulmonic insufficiency; estimated RVSP, 35 mm Hg
22	LAE; LVEF > 70%; MV abnormal with calcium in the mitral annulus posterior-laterally; posterior leaflet motion reduced; anterior leaflet thickened and calcific with decreased excursion; tricuspid and pulmonic valves normal; severe MR; mean pressure across the MV, 12 mm Hg; peak 22 mm Hg; mild pulmonic insufficiency and TR; RV systolic pressure, 38 mm Hg
24	Estimated LVEF 65%; valves normal; tricuspid regurgitation; estimated RV systolic pressure, 45 mm Hg
31	Mild concentric LVH; ejection fraction, 65%; normal flow across aortic and MV; mild TR with normal-to-high right-sided pressure
32	LVEF normal; mild MR and TR; pulmonary arterial systolic pressure estimated, 35–40 mm Hg

*Studies in 13 patients are based on medical history. The majority of patients had normal systolic function before transplantation, as indiated by gated pool study. MV = mitral valve; TV = tricuspid valve; LVH = left ventricular hypertrophy; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; PA = pulmonary artery; LVEF = left ventricular ejection fraction; RVG = radionucleotide ventriculography; LV = left ventricle/ventricular; RA = right atrium; MR = mitral regurgitation; RV = right ventricle/ventricular; AV = aortic valve; AI = aortic insufficiency; LAE = left atrial enlargement.

remained stable (changed by < 12%) in 3 of the 5 individuals who had a normal FVC at study entry (60%). It increased by ≥ 12% of the predicted value in two of these five patients (40%). Of the 15 other patients who achieved sustained remission and had entered the study with an abnormal FVC, the FVC increased by ≥ 12% of the predicted value in 12 of the 15 patients by 1 year following HSCT (80%). Two of these patients demonstrated a > 100% increase in total FVC over their baseline measurements. One additional patient, who remained free of active SLE and had not shown a significant improvement in FVC by 12 months after HSCT, achieved a 12% increase in predicted FVC by 24 months. Therefore, of the 15 patients with an abnormal FVC at study entry who achieved sustained freedom from active SLE, 13 of 15 patients (87%) had significantly improved FVC at follow-up (Table 3). In summary, 13 of the 15 patients who had an abnormal FVC, and remain without active lupus requiring therapy, have improved FVC (87%), whereas 1 of the 8 patients with persistent disease activity requiring therapy had transiently improved FVC (12%). Among these 28 patients, by 12 months after HSCT, the proportion of clinically significant improvement in FVC among patients without persistent SLE activity is statistically significantly higher than that among those patients with experienced persistent SLE activity (14 of 20 patients vs 1 of 8 patients, p = 0.0108). For a total 34 patients in this study, based on the analysis of the mixed-effect general linear model for repeated measurements, a statistically significant increasing trend in FVC over time was observed (p < 0.0001). With the adjustment for age and the status of disease, post-HSCT FVC statistically significantly increased at month 6 (n = 34; p = 0.0025), month 12 (n = 28; p < 0.0001), month 24 (n = 21; p < 0.0001), month 36 (n = 8; p = 0.0005), month 48 (n = 6; p = 0.0003), and month 60 (n = 5; p = 0.0006) compared with the pre-HSCT FVC. With the adjustment for age and month, no statistically significant difference was observed in FVC between patients with disease remission after HSCT and those patients without disease remission after HSCT (p = 0.7090).

Changes in DLCO following HSCT for individual patients are plotted in Figure 2. Two patients were unable to complete DLCO measurements in spite of best effort at pre-HSCT evaluation. Of the 28 patients who have now been monitored > 12 months after HSCT, 8 patients had persistent lupus activity requiring therapy (BILAG grade A). Twenty patients did not. Among the eight patients with persistent disease activity requiring therapy, DLCO was improved over 12 months in two patients (25%) and was stable in six patients (75%). Among the 20

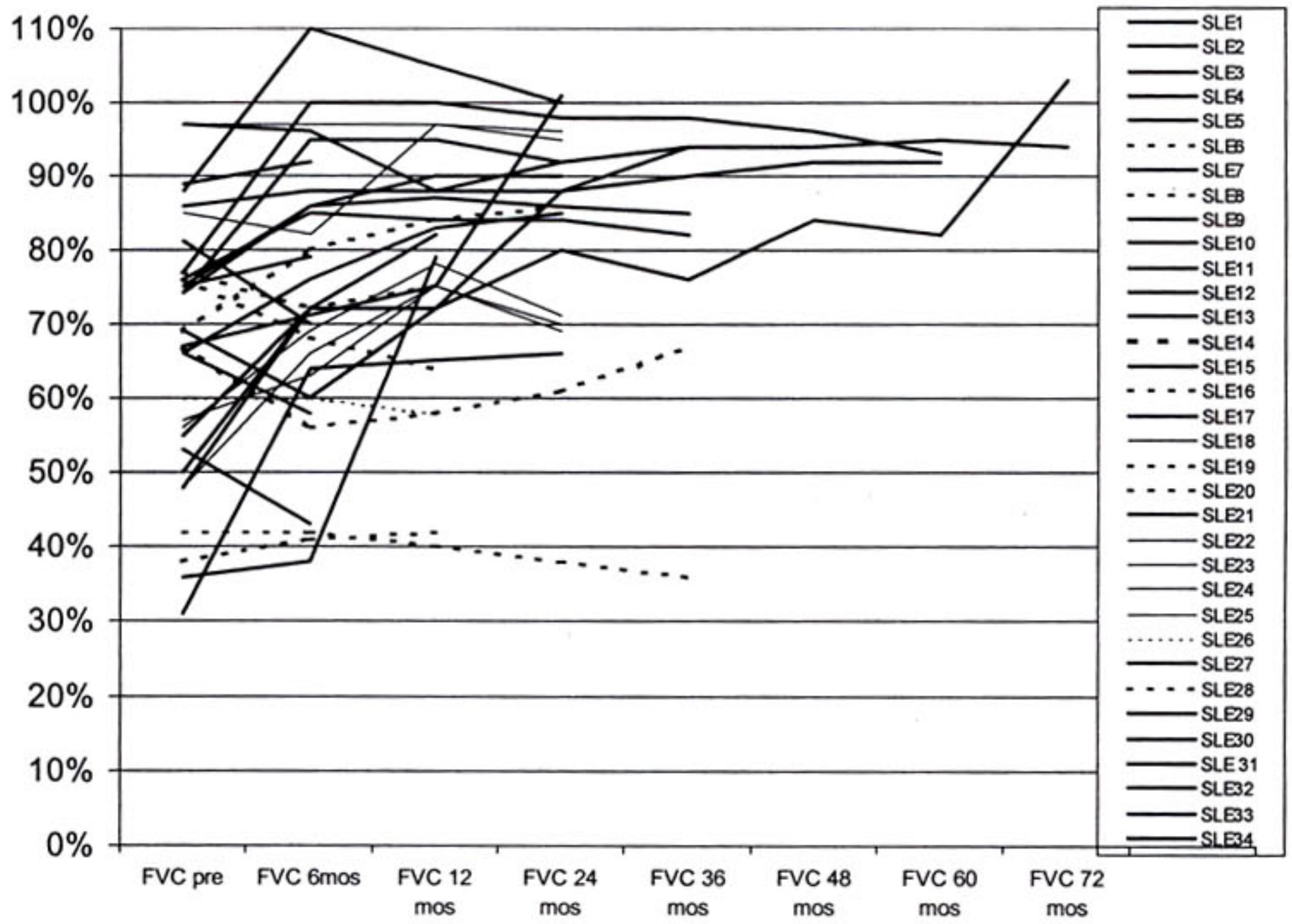

FIGURE 1. Change in FVC following HSCT in patients with SLE. Solid lines indicate lupus activity present; broken lines indicate persistent lupus activity.

patients with no disease activity on extended follow-up, 5 patients had normal DLCO at study entry and these 5 patients retained normal DLCO at 12 months after HSCT. Of the remaining 15 individuals with freedom from BILAG grade A, the DLCO increased by ≥ 12% of the predicted value in 11 of 15 patients by 1 year after HSCT (73%). Of the remaining four individuals without active SLE and abnormal DLCO at entry, who did not show improvement in DLCO by 12 months, three patients had improved by ≥ 12% of the predicted value by 2 years; the other patient has remained stable. Therefore, of the 20 individuals evaluated for > 1 year, who have experienced sustained freedom from active SLE, 93% of those with a low DLCO have improved (14 of 15 patients), 5 of the 5 patients with a normal DLCO stabilized, and 1 of 15 patients with an abnormal DLCO neither improved nor declined by 2 years (7%). In contrast, only two of the eight patients with persistent active lupus requiring therapy experienced an improved DLCO at 1 year (25%). Among these 28 patients, by 12 months after HSCT, no statistically significant difference was observed on the proportion of clinically significant improvement in DLCO between patients with and without persistent SLE activity (2 of 8 patients vs 11 of 20 patients, $p = 0.2213$). Statistically significant differences in the proportion of clinically significant improvement in DLCO, however, were observed between patients with persistent SLE activity, who had an abnormal DLCO at study entry and those who had an abnormal DLCO at study entry, and did not experience persistent SLE activity (2 of 8 patients vs 11 of 15 patients, $p = 0.0393$), and between patients who remained free of SLE activity and had a normal FVC at study entry and patients who remained free of SLE activity and had an abnormal FVC at study entry (0 of 5 patients vs 11 of 15 patients, $p = 0.0081$). For the total 34 patients in this study, based on the analysis of the mixed-effect general linear model for repeated measurements, a statistically significant increasing trend in DLCO over time was observed ($p < 0.0001$). With the adjustment of age and the status of disease, post-HSCT DLCO statistically significantly increased at month 6 ($n = 34$; $p = 0.0410$), month 12 ($n = 28$; $p < 0.0001$), month 24 ($n = 21$; $p < 0.0001$), month 36 ($n = 8$; $p < 0.0001$), month 48 ($n = 6$; $p = 0.0010$), and month 60 ($n = 5$; $p = 0.0006$) compared with the pre-HSCT DLCO. With the adjustment for age and month, no statistically significant difference in DLCO between patients with disease remission after HSCT and those patients without disease remission after HSCT ($p = 0.2755$).

The relationship of change in PFT results to survival is presented in Figure 3. The median pretreatment values for FVC and DLCO and their values 1 year after HSCT are presented in Figure 4, with the solid line indicating the sustained-remission patients and the dotted line indicating the persistent SLE-activity patients.

Table 3—*Follow-up Characteristics of Each of the 34 HSCT Recipients*

SLE Patient No.	Sustained Remission	Alive	Most Recent FEV_1 % Predicted	Most Recent FVC % Predicted	Most Recent TLC % Predicted	Most Recent Adjusted DLCO, % Predicted	Most Recent DLCO Adjusted for Volume Averaging, % Predicted	Most Recent Prednisone Dose, mg/d	Chemotherapy Administered at Any Time After HSCT, mo
1	Yes	Yes	78	103	92	60	76	None	40
2	Yes	Yes	89	94	Not done	78	107	None	None
3	Yes	Yes	85	92	92	87	121	None	None
4	Yes	Yes	83	93	95	88	92	None	None
5	Yes	Yes	79	82	79	54	78	None	None
6	No	Yes	37	36	55	33	67	None	Repeatedly
7	Yes	Yes	93	86	94	78	96	None	None
8	No	No	66	67	65	83	134	15	Repeatedly
9	Yes	Yes	89	85	Not done	50	77	None	None
10	Yes	Yes	88	92	Not done	Not done	Not done	None	None
11	Yes	Yes	81	66	76	67	90	None	26
12	Yes	Yes	102	88	Not done	81	100	None	None
13	Yes	Yes	83	95	Not done	96	99	None	None
14	No	Yes	159	154	120	127	Not done	None	None
15	Yes	Yes	77	72	71	83	110	None	None
16	No	No	65	64	65	29	62	60	11
17	Yes	Yes	Not done	79	Not done	59	89	None	None
18	Yes	Yes	81	75	83	66	104	None	None
19	No	Yes	84	86	82	53	70	40	12
20	No	No	47	42	51	49	107	20	14
21	Yes	Yes	83	83	96	87	103	None	None
22	Yes	Yes	98	96	96	53	58	None	None
23	Yes	Yes	71	65	72	57	89	None	None
24	Yes	Yes	62	67	69	41	66	None	None
25	Yes	Yes	87	83	84	58	81	None	None
26	No	No	Not done	58	Not done	40	Not done	60	11
27	Yes	Yes	115	110	92	83	92	None	None
28	No	Yes	77	75	Not done	40	Not done	30	None
29	Yes	Yes	100	92	92	72	103	None	None
30	Yes	Yes	47	43	Not done	Not done	Not done	None	None
31	Yes	Yes	72	70	74	48	75	None	None
32	Yes	Yes	59	58	71	48	82	None	None
33	Yes	Yes	85	79	87	48	60	None	None
34	Yes	Yes	79	70	67	41	72	None	None

Toxicity

There was no transplant-related mortality. All six patients who underwent transplantation in the last year are currently alive and free of supplemental oxygen use. Of the 28 patients who have been followed up for > 12 months after HSCT, 8 patients did not have remission from SLE; 6 of these patients also did not have an improvement in pulmonary function. Four of these eight individuals have died 13 to 36 months after HSCT from severe and refractory SLE activity. These deaths were secondary to SLE disease involving the brain and the lung in three cases and to sepsis following chemotherapy for severe mucocutaneous disease in the fourth case. The other four patients are receiving chemotherapy for persistent disease manifestations. Of the 20 patients with remission from disease with HSCT, 1 patient died of pneumonia 25 months after HSCT and was without evidence of active SLE. The other 19 patients are living 13 to 76 months after HSCT, and none are receiving chemotherapy.

Transplant-related toxicities included the following: one patient experienced hypotension during ATG infusion. She had received ATG previously, just 2 months prior at a referring institution. Acute pulmonary edema occurred in three patients and precipitated transfer to the medical ICUs due to hypoxia. Two of the medical ICU transfers required transient mechanical ventilation and continuous veno-veno hyperflitraton because of pulmonary edema. This occurred in spite of being maintained at hospital admission weight, but responded well to removal of fluid and achievement of low filling pulmonary pressures. Other acute nonpulmonary toxicities included Klebsiella bacteremia causing disseminated intravascular coagulation (one patient)

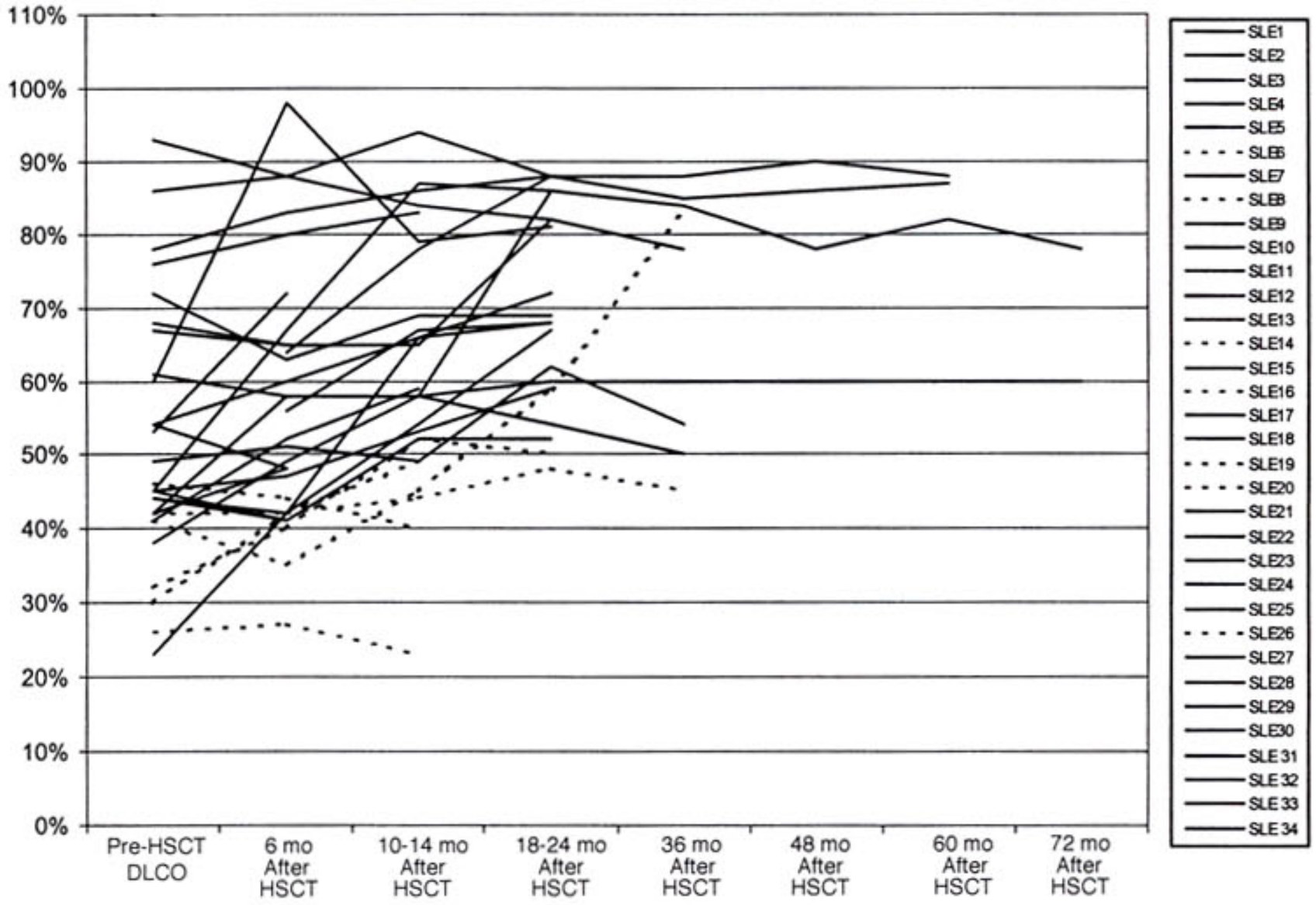

FIGURE 2. Change in DLCO prior to and following HSCT. Solid lines indicate significant lupus activity currently; broken lines indicate persistent SLE activity currently.

and two episodes of uncomplicated line-related staphylococcal bacteremia. Late infections included two incidents of pneumocystis pneumonia in individuals who had stopped their prophylaxis. There were three episodes of varicella zoster, confined to one or two dermatomes, both in individuals who had stopped their valacyclovir.

DISCUSSION

The prevalence and type of pulmonary dysfunction among SLE populations has been examined prospectively in both adults and children. High-resolution CT of the lung performed in 34 unselected lupus patients revealed a chronic interstitial

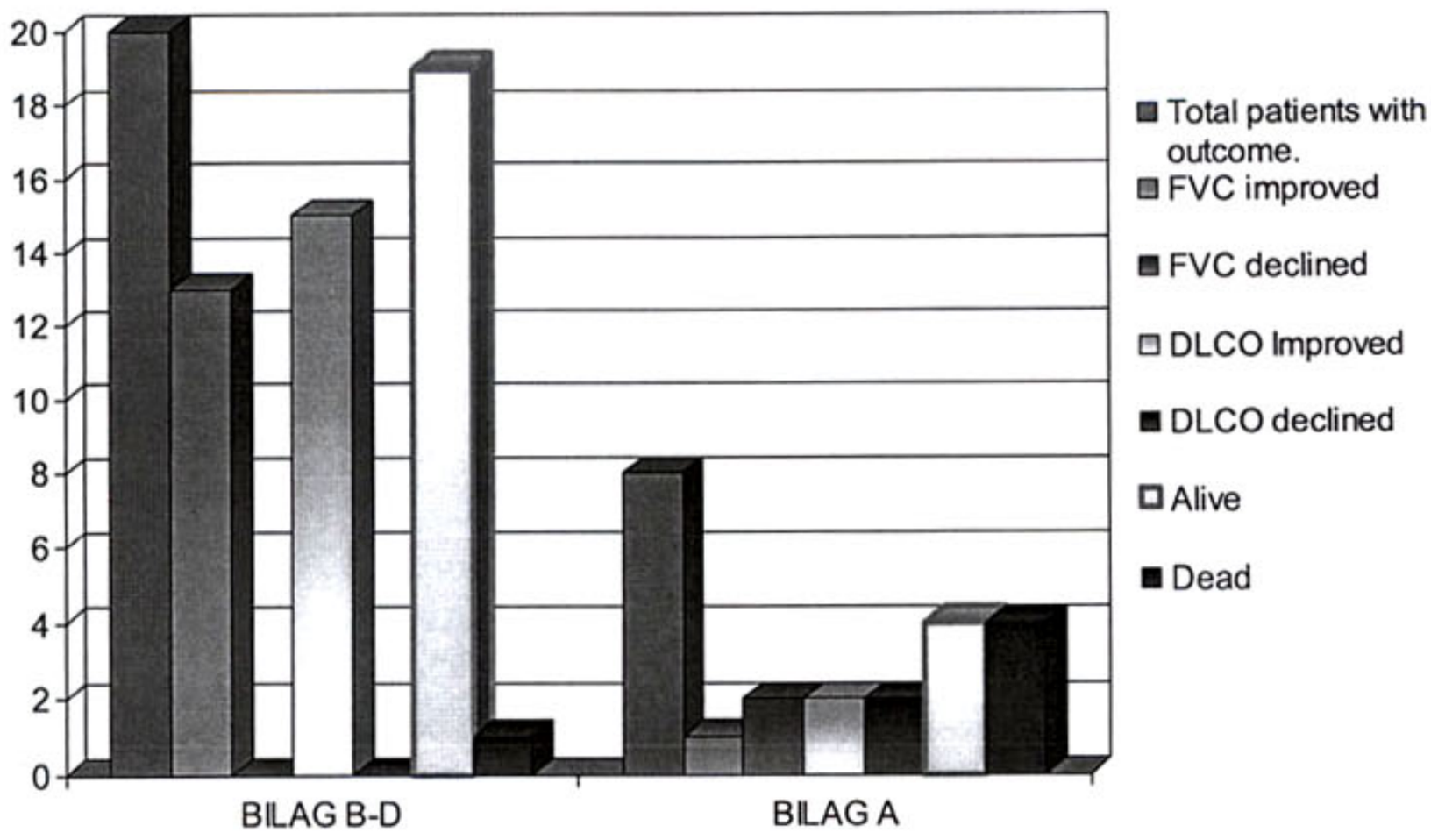

FIGURE 3. Changes observed in PFT results in the two major groups: those with sustained freedom from active SLE requiring treatment (BILAG grades B-D) after HSCT, and those requiring immune suppressive therapy (BILAG grade A) among the 28 patients now 13 to 77 months after HSCT.

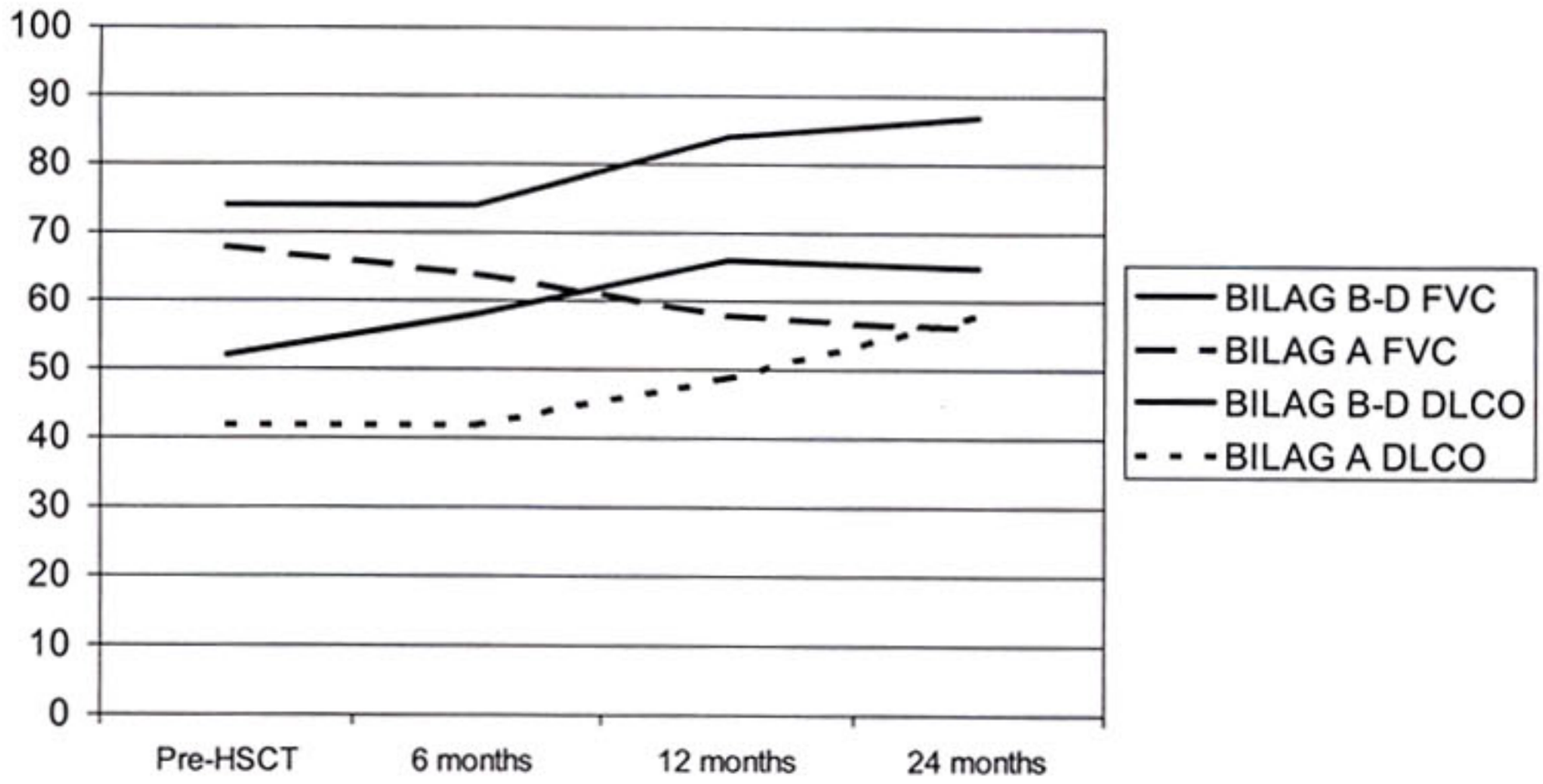

FIGURE 4. Median value of FVC and DLCO before HSCT and at stated intervals after HSCT in the two outcome groups: those with sustained remission from SLE (BILAG grades B-D; solid lines; n = 20) and those with persistent SLE activity requiring therapy (BILAG grade A; dashed lines; n = 8). Some of the improvement in DLCO in the BILAG grade A group is deceptive in that there were only three individuals contributing to the 24-month time point in the BILAG grade A group; three patients had died, one refused, and one in not 24 months after HSCT.

process in 11 patients (one third); 9 of these 11 patients denied pulmonary symptoms.[20] Twenty-four ambulatory adults with SLE, none of whom had overt respiratory symptoms, underwent PFTs in 1996; they were compared to 24 age-matched, healthy control subjects.[21] Compared to control subjects, SLE patients showed a significantly decreased TLC and DLCO and an increased arterial-alveolar oxygen gradient. DLCO impairment correlated best with disease activity, as measured by the European Consensus Lupus Activity Measurement.[21] In a separate study, 13 children with SLE underwent baseline evaluation of lung function, which was then repeated at a median of 4.5 years.[22] Abnormalities were correlated with disease activity, as measured by the Systemic Lupus Activity Measure. Diffusion was the most common abnormality among children and was an isolated abnormality in 45% of patients at baseline. These authors also found a correlation between disease activity and the degree of diffusion impairment. It appeared that in this group of children, whose disease activity was generally improved under close medical supervision, that the baseline finding of a diffusion abnormality did not predict a progression of lung functional impairment over time. While the improvements were modest, this is the only summary documenting a clear-cut sustained improvement in pulmonary function among individuals with SLE when disease activity is controlled over time.[22]

The data presented here confirm the very high prevalence of abnormal pulmonary function in severe SLE. The most frequently identified abnormality, low DLCO, was present in the vast majority of our patients, even those denying respiratory symptoms. These data support earlier data demonstrating that low DLCO is common when asymptomatic adults and children with SLE are screened for lung disease,[21,22] and that diffusion impairment can be seen in SLE patients with no radiographic finding.[3] Other causes of impaired diffusion include pulmonary embolism, interstitial lung disease, pulmonary hypertension, and anemia. While the DLCO adjustment for volume averaging diminished the percentage of patients with a significantly low DLCO value, we would not conclude that a true diffusion impairment or parenchymal disease is absent in these patients. Baseline data further confirm the common presence of a restrictive defect in pulmonary function. Again, there are multiple reasons for restriction in SLE: (1) corticosteroid-induced obesity, (2) corticosteroid-induced myopathy, (3) interstitial lung disease, (4) SLS, (5) myositis, (6) pulmonary hypertension, and (7) pleural effusions. Pleuritic chest pain from either a musculoskeletal source or pleuritis further reduces TLC and expiratory airflow.

The results of this study further demonstrate significant improvement in gas exchange, and FVC in SLE patients successfully treated with HSCT. The precise mechanism whereby HSCT improves lung function was not addressed in this study.

If improvement in pulmonary function can track lupus activity, can pulmonary function predict sustained remission from active disease in SLE? Seven patients have not had normal or significantly improved pulmonary function (FVC and/or DLCO) at

12 months following HSCT. Of these seven patients, four were showing signs of disease activity at their 12-month follow-up. Within the next 6 months, BILAG grade A developed in two more patients. Therefore, failure to achieve significant improvement or sustain normal lung function at 12 months was associated with relapse into BILAG grade A 86% of the time that it occurred. Of the 21 individuals with an improvement in one or more pulmonary function aspects or simply maintaining what had been normal baseline testing at 1 year, persistent SLE disease activity requiring therapy developed in only two patients (10%). Nineteen patients have remained free of BILAG grade A (90%).

In conclusion, pulmonary function abnormalities are extremely common among patients with refractory SLE. Successful treatment with HSCT improves lung function and allows for discontinuation of supplemental oxygen and systemic corticosteroids. Further studies are required to elucidate the mechanism underlying this benefit.

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