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BRIEF REPORT

Survival and Predictors of Mortality in Systemic Sclerosis–Associated Pulmonary Arterial Hypertension: Outcomes From the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry

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Objective. **To assess cumulative survival rates and identify independent predictors of mortality in patients with incident systemic sclerosis (SSc)–associated pulmonary arterial hypertension (PAH) who had undergone routine screening for PAH at SSc centers in the US.**

Methods. **The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma registry is a prospective registry of SSc patients at high risk for PAH or with definite pulmonary hypertension diagnosed by right-sided heart catheterization within 6 months of enrollment. Only patients with World Health Organization group I PAH (mean pulmonary artery pressure ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg without significant interstitial lung disease) were included in these analyses.**

Results. **In total, 131 SSc patients with incident PAH were followed for a mean ± SD of 2.0 ± 1.4 years. The 1-, 2-, and 3-year cumulative survival rates were 93%, 88%, and 75%, respectively. On multivariate analysis, age >60 years (hazard ratio [HR] 3.0, 95% confidence interval [95% CI] 1.1–8.4), male sex (HR 3.9, 95% CI 1.1–13.9), functional class (FC) IV status (HR 6.5, 95% CI 1.8–22.8), and diffusing capacity for carbon monoxide (DLCO) <39% predicted (HR 4.2, 95% CI 1.3–13.8) were significant predictors of mortality.**

Conclusion. **This is the largest study describing survival in patients with incident SSc-associated PAH followed up at multiple SSc centers in the US who had undergone routine screening for PAH. The survival rates were better than those reported in other recently described SSc-associated PAH cohorts. Severely reduced DLCO and FC IV status at the time of PAH diagnosis portended a poor prognosis in these patients.**

Introduction

Pulmonary arterial hypertension (PAH) as confirmed by right-sided heart catheterization (RHC) affects 8–12% of patients with systemic sclerosis (SSc; scleroderma) (1,2) and is associated with a >3-fold increased risk of death compared with SSc patients without PAH (3,4). Compared to patients with idiopathic PAH and other forms of con-

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Significance & Innovations

- The 1-, 2-, and 3-year cumulative survival rates were 93%, 88%, and 75%, respectively, in this multicenter US cohort of patients with incident systemic sclerosis (SSc)–associated pulmonary arterial hypertension (PAH) who had undergone routine screening for PAH.
- Severely decreased diffusing capacity for carbon monoxide and functional class IV status at the time of the PAH diagnosis portended a poor prognosis in SSc patients, particularly in older patients and in men.

nective tissue disease (CTD)–associated PAH (5), patients with SSc-associated PAH experience poorer outcomes. Despite the availability of several PAH-specific therapies, recent studies of patients with incident SSc-associated PAH have estimated 1- and 3-year survival rates ranging from 72–86% and 39–67%, respectively (1,3,6–8). Because several studies have indicated that early treatment of PAH can improve hemodynamics, exercise capacity, and survival (9–11), guidelines for the screening and early detection of PAH in SSc patients who are at high risk for PAH have been developed (12). The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry was established in 2006 to assess the outcomes of patients at high risk for developing PAH and of those with incident disease. The premise of the PHAROS registry is that early detection and close monitoring of PAH in SSc patients could improve health-related outcomes. Herein, we describe the cumulative survival rates and predictors of mortality in this cohort of patients with SSc-associated PAH followed up at specialized scleroderma centers throughout the US.

Patients and methods

The PHAROS registry is a longitudinal prospective registry involving 22 US scleroderma centers. The participating centers obtained institutional review board approval and all patients provided written informed consent prior to enrollment. The baseline characteristics and study design for the PHAROS registry have been described elsewhere (13).

The PHAROS registry enrolled SSc patients who were at high risk for developing pulmonary hypertension (PH; pre-PH) or who had definite PH diagnosed by RHC within 6 months of enrollment. Pre-PH patients must have fulfilled one of the following 3 criteria: 1) right ventricular systolic pressure (RVSP) on transthoracic echocardiogram (TTE) $\geq$40 mm Hg (calculated as the pressure gradient between the right ventricle and right atrium using the maximum velocity of the tricuspid regurgitant jet plus the right atrium pressure), 2) forced vital capacity (FVC) >70% predicted and diffusing capacity for carbon monoxide (DLCO) <55% predicted, or 3) %FVC:%DLCO ratio >1.6. All SSc patients at all centers were to undergo at least annual TTE and pulmonary function tests (PFTs) to screen for PAH at the time of registry enrollment. RHC was obtained in pre-PH patients as clinically indicated and determined by the treating physician. Patients with definite PH must have had a mean pulmonary artery pressure (PAP) $\geq$25 mm Hg at rest on RHC performed within the 6 months prior to enrollment into the registry. Only patients with World Health Organization (WHO) group I PAH ac-

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cording to the 2009 Dana Point Classification Criteria for PH, with a mean PAP ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg on RHC without significant interstitial lung disease defined as an FVC ≥65% predicted and no or only mild fibrosis on a high-resolution computed tomography (HRCT) scan of the chest, were included in this analysis. The pre-PH patients could be recategorized as having definite PH based on RHC over the course of the study, and these patients were included in this analysis.

A subgroup analysis of patients who received ≥3 continuous months of the same PAH-specific therapies over the first year of followup was performed. For this subgroup analysis, patients were divided into 4 different treatment categories based on the following initial PAH-specific therapy used as determined by the treating physicians: 1) endothelin receptor antagonist (ERA) monotherapy, 2) phosphodiesterase 5 (PDE-5) inhibitor monotherapy, 3) prostacyclin analogue (PCA) monotherapy, or 4) combination therapy with at least 2 PAH-specific therapeutic classes.

The following information was collected at baseline and on annual followup: demographics, medications, physical examination findings, New York Heart Association (NYHA) functional class (FC) assessment, serum autoantibodies, brain natriuretic peptide (BNP)/N-terminal proBNP levels if available, PFT results, TTE results, findings on HRCT, 6-minute walk distance (6MWD), and hemodynamics on RHC if performed. The primary outcome measure was death and the causes of death were recorded if known.

For statistical analysis, baseline characteristics were assessed by descriptive statistics. Kaplan-Meier curves were estimated for survival from the time of the first RHC at which PAH was confirmed. The differences in outcomes between subgroups were assessed by the log rank test. Cox regression models were used to identify significant predictors of mortality. DLCO, mean PAP, and pulmonary vascular resistance (PVR) were evaluated as categorical variables using the median value as the cut point. Demographic variables and those with a *P* value less than 0.1 in the univariate analyses were included in a multivariate model. Backward selection was used to determine the final model, retaining only variables with a *P* value less than 0.05.

For the analysis evaluating the effect of PAH-specific therapies on outcomes, Kaplan-Meier curves were estimated for 1-year survival from the time PAH-specific medication(s) were started, with differences between the treatment categories assessed by the log rank test.

Table 1. Baseline characteristics of patients with systemic sclerosis–associated pulmonary arterial hypertension in the PHAROS registry*

Clinical feature (no. of patients)	Value
Age, mean ± SD years (131)	60.4 ± 10.4
Women, no. (%) (131)	110 (84)
Race, no. (%) (131)	
White	108 (82)
African American	13 (10)
Other	10 (8)
Limited cutaneous systemic sclerosis, no. (%) (130)	92 (70)
Time from first Raynaud's phenomenon symptom, mean ± SD years (131)	14.4 ± 12.0
Time from first non–Raynaud's phenomenon symptom, mean ± SD years (131)	10.3 ± 9.2
Autoantibodies, no. (%) (123)	
Anticentromere antibodies	44 (35.8)
Anti–Scl-70 antibodies	9 (7.3)
Anti–RNA polymerase III antibodies	5 (4.1)
Anti–U1 RNP antibodies	7 (5.7)
Nucleolar pattern of ANAs	30 (24.4)
Positive ANAs alone	27 (22.0)
Negative	6 (4.9)
Creatinine, mean ± SD mg/dl (131)	1.0 ± 0.6
New York Heart Association functional class, no. (%) (128)	
I	24 (18.8)
II	48 (37.5)
III	49 (38.3)
IV	7 (5.5)
6-minute walk distance, mean ± SD meters (101)	339 ± 130
Pulmonary function tests, mean ± SD	
FVC% predicted (121)	82 ± 16
DLCO% predicted (116)	42 ± 16
FVC%:DLCO% ratio (116)	2.2 ± 0.9
Transthoracic echocardiogram	
Right ventricular systolic pressure, mean ± SD mm Hg (117)	61 ± 20
Pericardial effusion, no. (%) (111)	44 (39.6)
Right-sided heart catheterization, mean ± SD	
Mean pulmonary artery pressure, mm Hg (131)	36.5 ± 10.3
Pulmonary vascular resistance, WUs (123)	5.6 ± 3.4
Pulmonary capillary wedge pressure, mm Hg (131)	10.1 ± 3.3
Cardiac output, liters/minute (131)	5.0 ± 1.5

* PHAROS = Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma; ANAs = antinuclear antibodies; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; WUs = Wood units.

Results

Baseline characteristics. Of the 434 patients enrolled in the PHAROS registry at the time of this analysis, 131 had incident PAH as determined by RHC during the study, 14 of whom developed RHC-proven PAH after enrollment into the registry (Table 1). At the PAH diagnosis, the mean ± SD age was 60.4 ± 10.4 years and the mean ± SD disease duration from the first Raynaud's phenomenon and first non–Raynaud's phenomenon symptoms was 14.4 ± 12.0 and 10.3 ± 9.2 years, respectively. The majority of patients were women (84%), were white (82%), and had limited cutaneous disease (70%). Approximately one-third of the patients were anticentromere antibody positive, 7% were Scl-70 positive, 6% had an anti–U1 RNP antibody, 4% were RNA polymerase III positive, 24% had an antinuclear antibody (ANA) with an isolated nucleolar pattern without other scleroderma-specific antibodies, 22% had a positive ANA alone without a nucleolar pattern

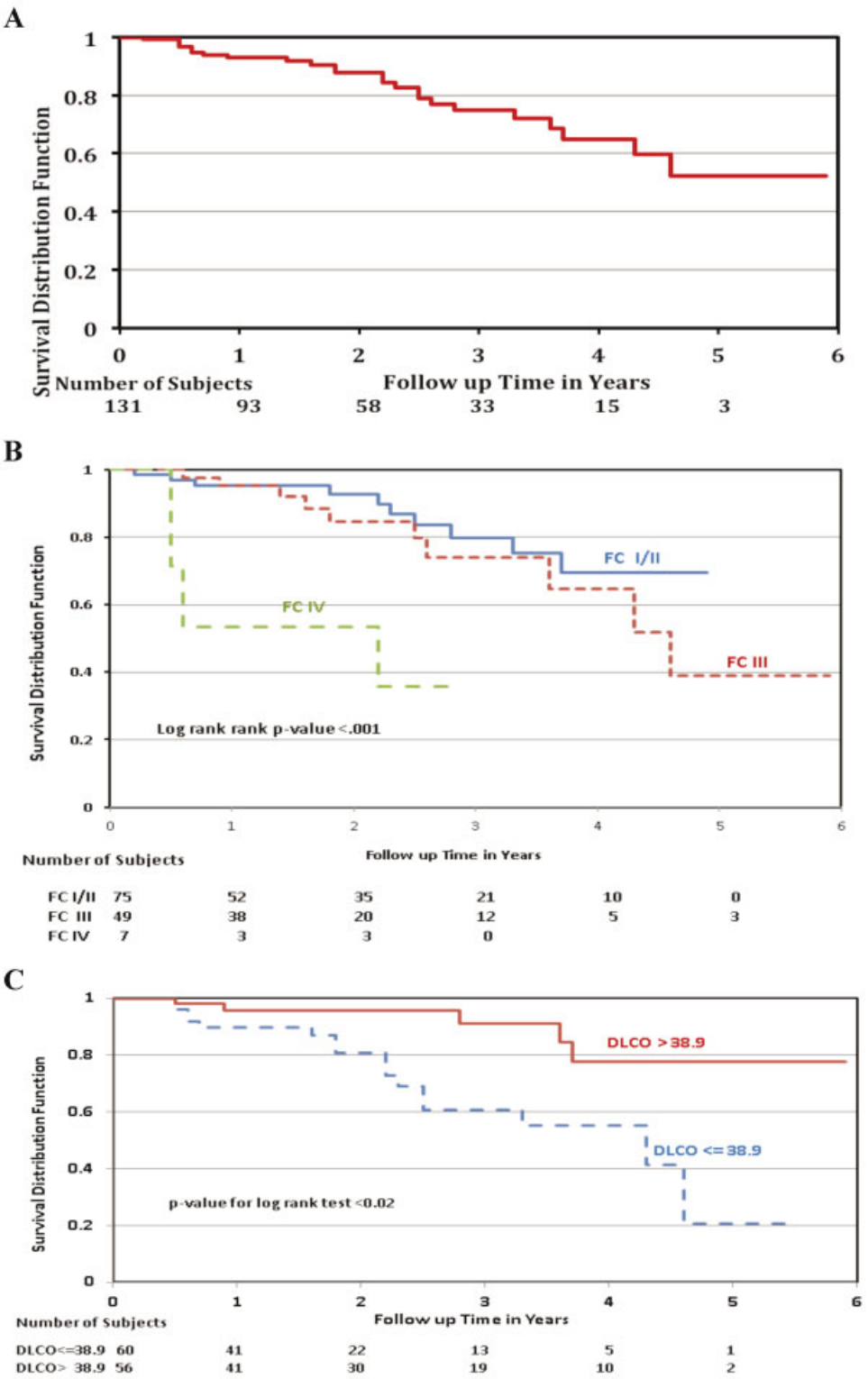

Figure 1. Survival in patients with systemic sclerosis (SSc)–associated pulmonary arterial hypertension (PAH) in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma registry. The 1-, 2-, and 3-year survival rates in the 131 patients with SSc-associated PAH were 93%, 88%, and 75%, respectively (**A**). New York Heart Association functional class (FC) IV status (**B**) and diffusing capacity for carbon monoxide (DLCO) ≤38.9% predicted (**C**) were associated with poorer survival.

or other scleroderma-specific antibodies, and 5% were negative for all autoantibodies. Only 2.3% of patients had a creatinine level >2 mg/dl at the time of RHC, and the median creatinine level was 0.9 mg/dl.

Table 2. Predictors of mortality using univariate and multivariate Cox regression analyses*

	Hazard ratio (95% CI)	*P*
Univariate (no. of patients)		
Age >60 years (131)	1.7 (0.7–3.8)	0.22
Male sex (131)	2.3 (0.9–6.4)	0.09
Nonwhite (131)	1.1 (0.4–3.0)	0.8
NYHA FC IV (128)	6.0 (2.0–18.2)	0.002
6MWD <165 meters (101)	2.5 (0.9–6.9)	0.09
Pericardial effusion (111)	1.1 (0.5–2.6)	0.9
DLCO <39% predicted (116)	4.3 (1.6–11.9)	0.005
Anticentromere antibody positive (123)	1.2 (0.5–2.9)	0.7
Mean PAP >35 mm Hg (117)	1.6 (0.7–3.6)	0.28
PVR >4.6 WUs (124)	3.4 (1.3–8.7)	0.01
Creatinine >0.9 mg/dl (124)	1.9 (0.8–4.5)	0.17
Multivariate (n = 85)		
Age >60 years	3.0 (1.1–8.4)	0.04
Male sex	3.9 (1.1–13.9)	0.03
NYHA FC IV	6.5 (1.8–22.8)	0.004
DLCO <39% predicted	4.2 (1.3–13.8)	0.02

* 95% CI = 95% confidence interval; NYHA FC IV = New York Heart Association functional class IV; 6MWD = 6-minute walk distance; DLCO = diffusing capacity for carbon monoxide; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; WUs = Wood units.

More than half of the patients were classified as having NYHA FC I (18%) or II (37%) status at the time of RHC, while only 5% of the patients were classified as having FC IV status. The mean ± SD RVSP on TTE was 61 ± 20 mm Hg, and 39.6% of the patients had a pericardial effusion. On baseline pulmonary evaluation, the mean ± SD DLCO was 42% ± 16% predicted and the mean ± SD 6MWD was 339 ± 130 meters. Half of the patients had a baseline DLCO <40% predicted, while only 11% of the patients had severely compromised exercise capacity, defined as a 6MWD <165 meters. The baseline hemodynamics were relatively mild, with a mean ± SD PAP of 36.5 ± 10.3 mm Hg (median 35), mean ± SD PVR of 5.6 ± 3.4 Wood units (WUs; median 4.6), and mean ± SD cardiac output of 5.0 ± 1.5 liters/minute.

Survival. In total, 24 patients (18%) died over a mean ± SD followup time of 2.0 ± 1.4 years (median 2.0 years [range 0–5.9 years]); 20 deaths (83%) were directly attributable to PAH or multiorgan failure related to underlying PAH. Other causes of death included new-onset scleroderma renal crisis (2 patients), infection (1 patient), and cancer (1 patient). The 1-, 2-, and 3-year survival rates in the overall SSc-associated PAH cohort were 93%, 88%, and 75%, respectively (Figure 1A).

Predictors of mortality. The univariate regression analysis identified FC IV status (hazard ratio [HR] 6.0, 95% confidence interval [95% CI] 2.0–18.2), DLCO <39% predicted (HR 4.3, 95% CI 1.6–11.9), and PVR >4.6 WUs (HR 3.4, 95% CI 1.3–8.7) as significant predictors of mortality (Table 2 and Figures 1B and C). On multivariate analysis, FC IV status (HR 6.5, 95% CI 1.8–22.8) and DLCO <39% predicted (HR 4.2, 95% CI 1.3–13.8) remained significant, while age >60 years (HR 3.0, 95% CI 1.1–8.4) and male sex (HR 3.9, 95% CI 1.1–13.9) were also independent predictors of mortality.

Effect of PAH-specific therapies on survival. Of the overall SSc-associated PAH cohort, 101 patients had received ≥3 continuous months of their initial PAH-specific therapies and ≥1 year of followup. The initial PAH treatment categories were as follows: ERA in 30%, PDE-5 in 48%, PCA in 13% (85% inhaled and 15% parenteral), and combination therapy in 10% of patients. Patients in the PCA group had a significantly lower mean ± SD DLCO at 29% ± 11% predicted compared with 45% ± 18%, 42% ± 14%, and 35% ± 11% in the PDE-5, ERA, and combination therapy groups ($P = 0.03$), respectively. Patients in the PCA group also had worse hemodynamics at the time of PH therapy initiation. The PCA group had a higher median mean PAP of 45 mm Hg (interquartile range [IQR] 40–45) compared with 35 mm Hg (IQR 29–40) in the PDE-5 group, 30 mm Hg (IQR 27–38) in the ERA group, and 38 mm Hg (IQR 33–53) in the combination therapy group ($P = 0.0008$). PCA patients also had a significantly higher mean ± SD PVR of 7.0 ± 2.8 WUs, compared with 4.8 ± 2.7 WUs for PDE-5, 3.7 ± 2.1 WUs for ERA, and 6.9 ± 2.1 WUs for combination therapy patients ($P = 0.0004$). The prostacyclin-treated patients clearly had worse hemodynamics, suggesting a sicker population. At 1 year, 7 patients (7%) who were receiving PAH-specific therapies died. The 1-year survival rate was significantly worse in the PCA group (69%) compared with the other treatment categories (ERA 97%, PDE-5 98%, and combination therapy 90%; $P = 0.002$).

Discussion

Our study described the outcomes of a large US SSc-associated PAH cohort of incident patients who had close

longitudinal followup at centers with a special interest in SSc. We found improved survival rates of 93% and 75% at 1 and 3 years, respectively, compared with other recently described SSc cohorts, including the US Registry to Evaluate Early and Long Term PAH Disease Management (REVEAL), which reported rates of 78% and 54% at 1 and 3 years, respectively (1,3,6–8). We recognize that a direct comparison of survival rates between the PHAROS registry and other cohorts is not possible; however, our cohort was enriched in patients with less severe disease (56% of patients with FC I and II status versus 23% in REVEAL), which was likely due to screening and early detection of PAH. In total, 17% of deaths were unrelated to PAH, highlighting that other comorbid conditions influenced outcome in SSc-associated PAH patients.

Our results concur with other smaller studies following early detection algorithms. Hachulla et al found 1- and 3-year survival rates of 100% and 80%, respectively, in 12 patients with SSc-associated PAH who were classified as having NYHA FC II status at diagnosis (10). Similarly, Humbert et al compared survival rates in 16 patients with SSc-associated PAH diagnosed in routine practice with 16 patients diagnosed following a systematic PAH detection program, with 1-, 3-, 5-, and 8-year survival rates of 75%, 31%, 25%, and 17%, respectively, in the former group compared with 100%, 81%, 73%, and 64%, respectively, in the early detection group (11). A recent Australian study of 117 patients with CTD-associated PAH had 1- and 3-year survival rates similar to ours (94% and 73%, respectively) (14). Although the latter cohort primarily comprised patients with SSc-associated PAH, better outcomes were observed in non-SSc patients with CTD-associated PAH (5,8), which may have skewed the results.

On multivariate analysis, we found that older age, male sex, NYHA FC IV status, and low DLCO were independent predictors of mortality. Similarly, Condliffe et al found that younger age, female sex, and a lower NYHA FC were protective in patients with SSc-associated PAH (8). A DLCO <39% predicted at PAH diagnosis was associated with a >4-fold increased risk of death in our cohort. Chandra et al found that a DLCO <43% predicted was associated with a lower HR of 2.4 (95% CI 1.1–5.0) in a cohort of 408 patients with WHO group I PAH, including 142 patients with CTD-associated PAH, but the number of SSc-associated PAH patients was not reported (15). Our results emphasize the importance of monitoring DLCO for both PAH screening and prognostic purposes in patients with SSc. Unlike other PAH studies, we did not find an increased risk of death associated with the presence of a pericardial effusion, NYHA FC III status, or low 6MWD, which may reflect the effect of multisystem disease manifestations in SSc on these variables.

The patients started on PCA as initial therapy had the poorest survival of all treatment groups, but this was likely confounded by more severe disease at baseline. Given the short length of followup, it is difficult to make definitive conclusions regarding treatment outcomes, and additional followup data are being collected.

We recognize that there are limitations to this study. Although our study was a prospective multicenter cohort, it was observational and therefore missing data were inevitable, particularly data on BNP/N-terminal proBNP levels. We also did not collect information on mean right atrial pressure, an important predictor of mortality in other SSc-associated PAH studies (1,14). Lead-time bias may have contributed to the improved survival rates observed in this population of patients with SSc-associated PAH who were diagnosed earlier with less severe disease due to existing PAH screening programs. Finally, PAH therapies were determined by the individual treating physicians, and not in a randomized controlled fashion.

Our study provided further evidence that early detection and management of PAH in SSc patients may lead to improved outcomes. Severely decreased DLCO and FC IV status at the time of PAH diagnosis portend a poor prognosis in SSc patients, particularly in older patients and men.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Chung, Domsic, Alkassab, Fischer, Silver, Steen.

Acquisition of data. Chung, Alkassab, Bolster, Csuka, Derk, Fischer, Frech, Furst, Gomberg-Maitland, Hinchcliff, Hsu, Hummers, Khanna, Medsger, Molitor, Preston, Schiopu, Shapiro, Silver, Simms, Varga, Gordon, Steen.

Analysis and interpretation of data. Chung, Domsic, Lingala, Alkassab, Fischer, Molitor, Simms, Gordon, Steen.

ROLE OF THE STUDY SPONSORS

Actelion and Gilead had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Actelion and Gilead.

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