Longterm Efficacy and Safety of Monotherapy versus Combination Therapy in Systemic Sclerosis–associated Pulmonary Arterial Hypertension: A Retrospective RESCLE Registry Study

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ABSTRACT. ***Objective.*** Monotherapy is an option as first-line therapy for pulmonary arterial hypertension (PAH). However, combination therapy is a beneficial alternative. Our objective was to evaluate the efficacy of monotherapy versus combination therapy in patients with systemic sclerosis (SSc)–associated PAH.

Methods. All patients with SSc-associated PAH from the Spanish Scleroderma Registry (RESCLE) were reviewed. Patients were split into 3 groups: monotherapy versus sequential combination versus upfront combination therapy. The primary endpoint was death from any cause at 1, 3, and 5 years from PAH diagnosis.

Results. Seventy-six patients (4.2%) out of 1817 had SSc-related PAH. Thirty-four patients (45%) were receiving monotherapy [endothelin receptor antagonist (n = 22; 29%) or phosphodiesterase-5 inhibitors (n = 12; 16%)], 25 (33%) sequential combination, and 17 (22%) upfront combination therapy. A lower forced vital capacity/DLCO in the sequential combination group was reported (2.9 ± 1.1 vs 1.8 ± 0.4 vs 2.3 ± 0.8; p = 0.085) and also a higher mean pulmonary arterial pressure in combination groups (37.2 ± 8.7 mmHg vs 40.8 ± 8.8 vs 46 ± 15.9; p = 0.026) at baseline. Treatment regimen (p = 0.017) and functional class (p = 0.007) were found to be independent predictors of mortality. Sequential combination therapy was found to be an independent protective factor (HR 0.11, 95% CI 0.03–0.51; p = 0.004), while upfront combination therapy showed a trend (HR 0.68, 95% CI 0.23–1.97; p = 0.476). Survival from PAH diagnosis among monotherapy, sequential, and upfront combination groups was 78% versus 95.8% versus 94.1% at 1 year, 40.7% versus 81.5% versus 51.8% at 3 years, and 31.6% versus 56.5% versus 34.5% at 5 years (p = 0.007), respectively. Side effects were not significantly different among groups.

Conclusion. Combination sequential therapy improved survival in our cohort. (First Release August 1 2019; J Rheumatol 2020;47:89–98; doi:10.3899/jrheum.180595)

Key Indexing Terms:
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Systemic sclerosis (SSc) is a connective tissue disease (CTD) of unknown origin. Pulmonary arterial hypertension (PAH) is one of the most devastating complications of SSc, with a prevalence of 12–13%[1,2,3,4,5]. Left untreated, PAH leads to right ventricular failure and death. Its prognosis is worse than idiopathic (IPAH)/familial PAH and other CTD-related PAH, and it is one of the main SSc-related causes of death[6,7,8]. SSc-related PAH survival has improved since the 1980s owing to better disease knowledge, screening programs, and emerging therapies[9,10,11,12,13]. However, mortality is still high.

Monotherapy remains an option for PAH treatment[14,15,16] recommended in guidelines[17] as first-line therapy for World Health Organization functional class (FC) II–III patients, with the same grade of evidence and recommendation (IA–IB) for endothelin receptor antagonists (ERA) and phosphodiesterase-5 (PDE5) inhibitors.

Combination therapy, targeting several of the main pathways that contribute to physiopathology of PAH (endothelin-1, prostacyclin, and nitric oxide), is gaining evidence. Although in guidelines[17] the grade of evidence and recommendation for combination therapy is the same as for monotherapy, more recent reports, including the AMBITION trial[18] and its posthoc analysis[19], which focused on CTD-PAH patients, suggest combination therapy as a better option to treat PAH, demonstrating its superiority regarding morbidity and mortality.

Our study was designed to evaluate the longterm efficacy and safety of combination therapy with PDE5 inhibitors and ERA versus monotherapy in a large Spanish nationwide SSc-related PAH cohort. Moreover, mortality's effect was compared between different treatment regimens.

MATERIALS AND METHODS

Study design. This was a retrospective cohort study. Data were obtained from the Spanish Scleroderma Registry (RESCLE), a project of the Autoimmune Diseases Working Group (GEAS) within the Spanish Society of Internal Medicine. The study includes patients with SSc who fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism criteria and/or the modified criteria proposed by LeRoy and Medsger in 1988, to avoid missing patients with SSc sine scleroderma or limited cutaneous SSc who could not fulfill the 2013 ACR criteria. Data were collected retrospectively until 2006 and prospectively onward. Thirty hospitals nationwide participated in the registry and 1817 patients were recorded. All participant centers obtained local ethics committee approval. We received ethics board approval of our institution (Bellvitge University Hospital, Barcelona, Spain, ref. PR126/13) as well.

Inclusion criteria were patients with SSc aged 18 years or more, with a diagnosis of PAH by right heart catheterization (RHC) with a mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg, a pulmonary capillary wedge pressure of ≤ 15 mmHg, and a pulmonary vascular resistance of > 3 Wood units, without interstitial lung disease (ILD) or with moderate ILD [defined by forced vital capacity (FVC) > 60% and not significant interstitial pattern on high-resolution computed tomography (HRCT)]. Ongoing treatment with prostanoids was the only exclusion criterion. Patients gave informed consent to participate in the RESCLE database. All centers included in the registry received their ethics board approvals.

The patient population was split into 3 groups according to treatment regimen: (1) monotherapy with ERA or PDE5 inhibitors; (2) sequential combination therapy, defined by ≥ 12 weeks between initiation of first and second drug; and (3) upfront combination therapy, defined by < 12 weeks between first and second drug. Cutoff point of 12 weeks was used in accordance with guidelines recommendations of reassessment[17] and because of the design of most trials with monotherapy, which evaluate results at 12 weeks to decide effectiveness of treatment or whether escalated treatment is needed[14,15,16]. Further, in the AMBITION trial, full doses of an upfront combination therapy with ambrisentan plus tadalafil were achieved in 8 weeks, so 12 weeks seemed an adequate limit to classify retrospectively upfront combination therapies as well[18].

Clinical and laboratory data among groups were compared, including demographic data, age at which the first digital ulcer appeared, time from SSc diagnosis, time from first SSc symptom, SSc disease subtype, New York Heart Association (NYHA) FC, visceral involvement, antibody profile, pulmonary functional tests (PFT), echocardiography measures, and hemodynamic variables in RHC.

Outcomes. Primary endpoint was death from any cause at 1, 3, and 5 years from SSc-related PAH diagnosis. The cause of death was recorded and compared among the 3 different treatment groups. Additionally, side effects attributable to medication were collected and compared.

Statistical analyses. All data were presented as absolute number and percentage for categorical variables, and mean ± SD for quantitative variables. Categorical variables were analyzed using chi-square test, and

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quantitative variables were analyzed with ANOVA. The Bonferroni correction was applied for multiple comparisons among categorical variables. A univariate and multivariate Cox proportional hazards model was performed to evaluate risk factors associated to mortality. Differences in mortality depending on the treatment prescribed were graphically shown by using Kaplan-Meier curves with their log-rank test. A p value < 0.05 was considered statistically significant. No loss to followup was reported.

RESULTS

Seventy-six patients with SSc-related PAH treated with ERA, PDE5 inhibitors, or both were identified among 1817 patients with SSc from the RESCLE database, diagnosed between 2002 to 2016, except for 1 case diagnosed in 1997. Of those, 34 (45%) were receiving monotherapy with ERA (22 patients; 29%) or PDE5 inhibitors (12 patients; 16%). Sequential combination therapy was given to 25 patients (33%) and upfront combination therapy was initiated in 17 patients (22%).

General data among groups. Out of the 76 patients included, 69 (91%) fulfilled the 2013 ACR criteria and the remaining 7 (9%) fulfilled the 1988 LeRoy and Medsger criteria.

In all SSc-related PAH groups, either under monotherapy, sequential, or upfront combination therapy, most patients were female [28 patients (82%) vs 23 (92%) vs 14 (82%); p = 0.532]. The study did not find differences in smoking behavior. For current smokers, there was 1 patient (3%) versus 2 (8.3%) versus 1 (6.7%; p = 0.674); former smokers, 6 patients (18%) versus 4 (17%) versus 4 (27%; p = 0.722); and never smokers, 26 patients (79%) versus 18 (75%) versus 10 (67%; p = 0.668). The age at onset of SSc was around 50 years (48.5 ± 14.9 yrs vs 51.7 ± 15 yrs vs 48 ± 15.8 yrs; p = 0.694) and the age at diagnosis of SSc close to 60 years (58.9 ± 15.6 yrs vs 59.6 ± 14.9 yrs vs 57.7 ± 13.4 yrs; p = 0.927). Thus, the delay from the onset of the disease to the time of diagnosis was shorter in the sequential combination therapy group but did not reach statistical significance (11.8 ± 12.6 yrs vs 5.8 ± 9.8 yrs vs 10.3 ± 17.2 yrs; p = 0.277). The mean followup from the first symptom of SSc was 20.9 ± 12.5 years versus 16.9 ± 10.3 years versus 17.7 ± 15.9 years (p = 0.511), and the mean followup from the diagnosis of SSc was 9.8 ± 8.3 years versus 9.7 ± 7.4 years versus 8.5 ± 7.8 years (p = 0.851) for monotherapy versus sequential combination therapy versus upfront combination therapy, respectively. Regarding PAH, the time from first SSc symptom until definitive PAH diagnosis was 19.5 ± 12.8 years versus 11.6 ± 11.7 versus 16.6 ± 16.4 (p = 0.157), with statistically significant results comparing monotherapy with sequential combination (p = 0.040). More than 90% of patients met the 2013 ACR criteria [26 patients (93%) vs 22 (96%) vs 14 (100%); p = 0.581]. No differences among groups were found according to the SSc subset. They were classified as lcSSc in 22 patients (65%) versus 16 (64%) versus 9 (56%; p = 0.835); dcSSc in 6 patients (18%) versus 5 (20%) versus 4 (25%; p = 0.832); and sine scleroderma in 6 patients (18%) versus 4 (16%) versus 3 (19%; p = 0.973) for monotherapy, sequential combination, and upfront combination therapy, respectively (data not shown).

Features among groups showed no differences (Table 1) related to serologic profile, capillaroscopy, and visceral involvement, with the exception of pericardial involvement, which was more present in the upfront combination therapy group. The Bonferroni correction confirmed statistical significance in pericardial involvement between upfront combination versus monotherapy and sequential combination therapy. Although it did not reach statistical significance, the percentage of ILD was different between groups, with 59% versus 80% versus 76.4% for monotherapy, sequential combination, and upfront therapy, respectively. Of those, the majority of patients had moderate ILD as defined earlier, with 55% versus 70% versus 58% for monotherapy, sequential combination, and upfront therapy, respectively.

Functional status among groups at baseline. FC among groups at baseline, PFT, echocardiography, and RHC findings are shown in Table 2. It was noteworthy that a lower %FVC/%DLCO was present in the sequential combination therapy group (2.9 ± 1.1 vs 1.8 ± 0.4 vs 2.3 ± 0.8; p = 0.085) and also a worse mPAP in both sequential and upfront combination therapy groups (37.2 ± 8.7 mmHg vs 40.8 ± 8.8 vs 46 ± 15.9; p = 0.026). The Bonferroni correction confirmed statistical significance in mPAP between upfront combination versus monotherapy.

Risk factors of mortality. In our univariate study, these were considered risk factors of mortality: the prescribed treatment regimen, FC class at PAH diagnosis, %FVC/%DLCO ratio, and the change in the tricuspid regurgitation velocity (TRV; Table 3).

After a multivariate analysis, the prescribed treatment regimen (p = 0.032) and FC at baseline (p = 0.007) were found independent predictors for longterm mortality (Table 3). Taking monotherapy as reference treatment, sequential combination therapy was found to be a protective factor (HR 0.23, 95% CI 0.07–0.69; p = 0.009) and upfront combination therapy showed a tendency of protection, without reaching statistical significance (HR 0.72, 95% CI 0.25–2.07, p = 0.541).

Survival and causes of death among groups. Longterm survival rates from diagnosis of SSc-related PAH among groups for monotherapy, sequential combination, and upfront combination therapy were, respectively, as follows: 78% versus 95.8% versus 94.1% at 1 year, 40.7% versus 81.5% versus 51.8% at 3 years, and 31.6% versus 56.5% versus 34.5% at 5 years (log-rank test, p = 0.007). Data on survival and patients at risk are shown in Table 4 and Kaplan-Meier curves are shown in Figure 1.

Twenty-six patients (34.2%) died during the followup. The causes of mortality among groups are shown in Table 5. Conditions secondary to SSc-related PAH were the main causes of death in all groups [7 patients (41.2%) vs 2 (50%) vs 3 (60%); p = 0.749].

Side effects among groups. Side effects were not significantly

Table 1. General features among groups.

Variables	Monotherapy	Sequential Combination	Upfront Combination	Global p	p, Monotherapy vs Sequential	p, Monotherapy vs Upfront
Patients, n	34	25	17			
Peripheral vascular involvement						
Raynaud phenomenon	32 (97)	22 (88)	15 (94)	0.402	0.305	1.000
Digital ulcers	14 (42)	12 (48)	9 (56)	0.659	0.791	0.542
Telangiectasia	24 (71)	18 (72)	12 (75)	0.949	1.000	1.000
Acroosteolysis	1 (5.3)	3 (23)	0	0.162	0.279	1.000
Musculoskeletal involvement	14 (41)	12 (50)	6 (40)	0.757	0.596	1.000
Calcinosis	7 (21)	6 (24)	1 (6.7)	0.377	0.762	0.406
Arthritis	5 (26)	3 (23)	1 (14)	0.812	1.000	1.000
Myositis	3 (16)	3 (23)	3 (43)	0.348	0.666	0.293
Tendon friction rubs	1 (5.3)	0	0	0.583	1.000	1.000
Joint contractures	6 (21)	6 (29)	4 (27)	0.837	0.739	0.719
Digestive involvement	25 (74)	17 (74)	12 (75)	0.994	1.000	1.000
Esophagus	22 (65)	15 (65)	10 (63)	0.984	1.000	1.000
Gastric	6 (25)	3 (18)	3 (25)	0.837	0.711	1.000
Intestinal	4 (17)	4 (24)	3 (25)	0.797	0.698	0.664
Malabsorption	4 (17)	3 (15)	3 (21)	0.883	1.000	1.000
Lung involvement	34 (100)	25 (100)	17 (100)	1.000	1.000	1.000
ILD	20 (59)	20 (80)	13 (76)	0.171	0.100	0.352
Heart involvement	16 (47)	12 (50)	5 (31)	0.468	1.000	0.365
Pericardial effusion	9 (26)	4 (16)	4 (24)	0.629	0.526	1.000
Pericarditis	2 (5.9)	3 (12)	5 (29)	0.063	0.641	0.034
Ischemia	5 (15)	4 (16)	1 (5.9)	0.596	1.000	0.650
Conduction alteration	9 (26)	7 (28)	2 (12)	0.419	1.000	0.297
Diastolic dysfunction	17 (50)	10 (40)	6 (35)	0.556	0.598	0.381
Renal involvement	4 (12)	2 (8.3)	3 (19)	0.611	1.000	0.666
Scleroderma renal crisis	0	0	1 (6.3)	0.159	1.000	0.320
Cancer	6 (18)	5 (20)	4 (24)	0.883	1.000	0.714
Capillaroscopy	25 (83)	19 (83)	11 (85)	0.988	1.000	1.000
Slow pattern	12 (48)	9 (47)	7 (64)	0.640	1.000	0.481
Active pattern	7 (28)	7 (37)	3 (27)	0.786	0.745	1.000
Normal/undetermined pattern	6 (24)	3 (16)	1 (9.1)	0.534	0.710	0.400
Immunological features						
ANA+	32 (94)	25 (100)	17 (100)	0.281	0.503	1.000
ATA+	7 (23)	2 (8.3)	3 (19)	0.367	0.271	0.753
ACA+	20 (65)	11 (48)	9 (56)	0.470	0.272	0.471
Anti-RNAP-III+	0	1 (13)	1 (13)	0.543	0.471	1.000
Anti-RNP+	1 (3.4)	1 (4.3)	0	0.701	1.000	0.714

Values are n (%) unless otherwise specified. ILD: interstitial lung disease; ANA: antinuclear antibody; ATA: antitopoisomerase I antibody; ACA: anticentromere antibody; anti-RNAP-III: anti-RNA polymerase III antibody.

different among groups [10 patients (29%) vs 8 (32%) vs 2 (12%); p = 0.295]. The most frequent side effects were edema, anemia, hepatotoxicity, arterial hypotension, and headache attributed to ERA; and rash, headache, and hepatotoxicity due to PDE5 inhibitors.

DISCUSSION

In our study, we evaluated longterm efficacy and safety of monotherapy versus combination therapy for PAH in a large Spanish SSc patient cohort. Results showed better longterm survival rates for the overall combination therapy groups. Moreover, sequential combination therapy showed superiority against monotherapy as a longterm protective factor in such population, while upfront combination therapy showed a tendency of protection without reaching statistical significance. Although more drugs were used in combination therapy groups, no safety differences were found between treatment regimens.

Results from previous studies reporting SSc-related PAH survival from PAH diagnosis are heterogeneous with regard to NYHA FC, PAH-specific regimens used, inclusion of incident or prevalent patients, and inclusion of some degree of ILD. Mukerjee, *et al*[2] conducted a prospective study including 722 patients with PAH FC III–IV diagnosed by RHC between 1998 and 2002, including 79 SSc-associated PAH patients, with survival at 1 and 3 years of 81% and 56%, respectively. Williams, *et al* demonstrated better survival since introduction of bosentan comparing 2 cohorts of

Table 2. Functional class, echocardiography, PFT, and hemodynamic variables at baseline.

Variables	Monotherapy	Sequential Combination	Upfront Combination	Global p	p, Monotherapy vs Sequential	p, Monotherapy vs Upfront
Functional class						
I	6 (18)	4 (17)	2 (13)	0.897	1.000	1.000
II	9 (26)	6 (25)	6 (38)	0.654	1.000	0.514
III	13 (38)	11 (46)	8 (50)	0.701	0.598	0.543
IV	2 (5.9)	1 (4.2)	0	0.616	1.000	1.000
FVC, %	67.6 ± 19.6	71.7 ± 22.6	59.7 ± 23.8	0.500	0.661	0.403
DLCO, %	25.3 ± 13.5	43.6 ± 18.6	38.1 ± 16.9	0.183	0.080	0.218
FEV1, %	63.4 ± 6.8	63.3 ± 6.8	64.7 ± 6.7	0.894	0.988	0.664
FVC/DLCO	2.9 ± 1.1	1.8 ± 0.4	2.3 ± 0.8	0.085	0.043	0.365
sPAP by echocardiography, mmHg	62.2 ± 21.5	64.0 ± 14.3	79.3 ± 31.9	0.260	0.834	0.152
TRV, m/s	3.7 ± 0.7	3.7 ± 0.6	3.9 ± 1.0	0.798	0.973	0.532
TAPSE, mm	19.5 ± 1.3	20.5 ± 2.1	13.1 ± 9.6	0.319	0.495	0.275
Pericardial effusion	3 (19)	2 (22)	4 (50)	0.248	1.000	0.167
Right ventricular dilation	7 (44)	5 (56)	4 (67)	0.608	0.688	0.635
mPAP, mmHg	37.2 ± 8.7	40.8 ± 8.8	46.0 ± 15.9	0.026	0.120	0.046
PCWP, mmHg	12.8 ± 6.2	11.1 ± 4.1	14.2 ± 5.0	0.254	0.303	0.467
Cardiac output, l/min	4.2 ± 1.3	4.3 ± 1.7	4.2 ± 1.7	0.963	0.775	0.898
PVR, Wood units	8.2 ± 5.9	8.1 ± 3.8	8.3 ± 4.9	0.994	0.947	0.966

Values are mean ± SD or n (%) unless otherwise specified. PFT: pulmonary functional tests; FVC: forced vital capacity; FEVI: forced expiratory volume in the first second; sPAP: systolic pulmonary arterial pressure; TRV: tricuspid regurgitation velocity; TAPSE: tricuspid annular plane systolic excursion; mPAP: mean PAP; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

Table 3. Risk factors associated with mortality.

Variables	Univariate Analysis, HR (95% CI)	p	Multivariate Analysis, HR (95% CI)	p
Time onset-diagnosis PAH	1.03 (0.99–1.07)	0.073	–	
Sex, female	0.63 (0.24–1.69)	0.363	–	
Age per 10-yr change	1.14 (0.76–1.73)	0.524	–	
SSc subset (limited + sine scleroderma)	1.58 (0.66–3.78)	0.300	–	
Treatment		0.016		0.032
Monotherapy	1 (ref.)	–	1 (ref.)	–
Sequential combination therapy	0.20 (0.07–0.61)	0.004	0.23 (0.07–0.69)	0.009
Upfront combination therapy	0.59 (0.22–1.60)	0.302	0.72 (0.25–2.07)	0.541
Functional class		0.003		0.007
I	1 (ref.)	–	1 (ref.)	–
II	1.00 (0.32–3.09)	0.994	1.20 (0.37–3.87)	0.765
III	1.04 (0.38–2.80)	0.943	1.24 (0.45–3.39)	0.675
IV	12.93 (2.90–57.62)	0.001	12.18 (2.71–54.69)	0.001
FVC per 10% of predicted change	0.86 (0.64–1.16)	0.316	–	
DLCO per 10% of predicted change	0.25 (0.05–1.13)	0.071	–	
FVC/DLCO per 10% of predicted change	683.65 (1.89–247508.97)	0.030	–	
sPAP per TTE per 10-mmHg change	1.43 (0.94–2.17)	0.095	–	
TTE per 1 m/s change	9.36 (1.74–50.34)	0.009	–	
TAPSE per 10-mm change	0.17 (0.02–1.23)	0.078	–	
Pericardial effusion	1.64 (0.50–5.38)	0.417	–	
Right ventricular dilation	2.10 (0.63–7.01)	0.226	–	
mPAP	1.02 (0.99–1.05)	0.242	–	
RAP	1.00 (0.86–1.16)	0.995	–	

PAH: pulmonary arterial hypertension; SSc: systemic sclerosis; FVC: forced vital capacity; sPAP: systolic pulmonary arterial pressure; mPAP: mean PAP; TTE: transthoracic echocardiography; TAPSE: tricuspid annular plane systolic excursion; RAP: right atrial pressure.

patients with SSc-associated PAH in FC III–IV without significant ILD, showing 1- and 2-year survival of 68% and 47%, respectively, in the historical cohort (before 2002) and 81% and 71%, respectively, in the contemporary cohort[12]. Fisher, *et al* reported a 1- and 3-year survival of 87.7% and 48.9%, respectively, in 50 patients with SSc-associated PAH

Table 4. Survival and patients at risk among groups, from the diagnosis of PAH.

Survival	4 Weeks	26 Weeks	52 Weeks	104 Weeks	156 Weeks
Monotherapy	0.970	0.878	0.780	0.645	0.407
Sequential combined therapy	1.000	0.958	0.958	0.958	0.815
Upfront combined therapy	1.000	0.941	0.941	0.776	0.518
Patients at risk	**0–4 Weeks**	**4–26 Weeks**	**26–52 Weeks**	**52–104 Weeks**	**104–156 Weeks**
Monotherapy	33	31	27	23	17
Sequential combined therapy	25	25	23	22	20
Upfront combined therapy	17	17	14	12	7

PAH: pulmonary arterial hypertension.

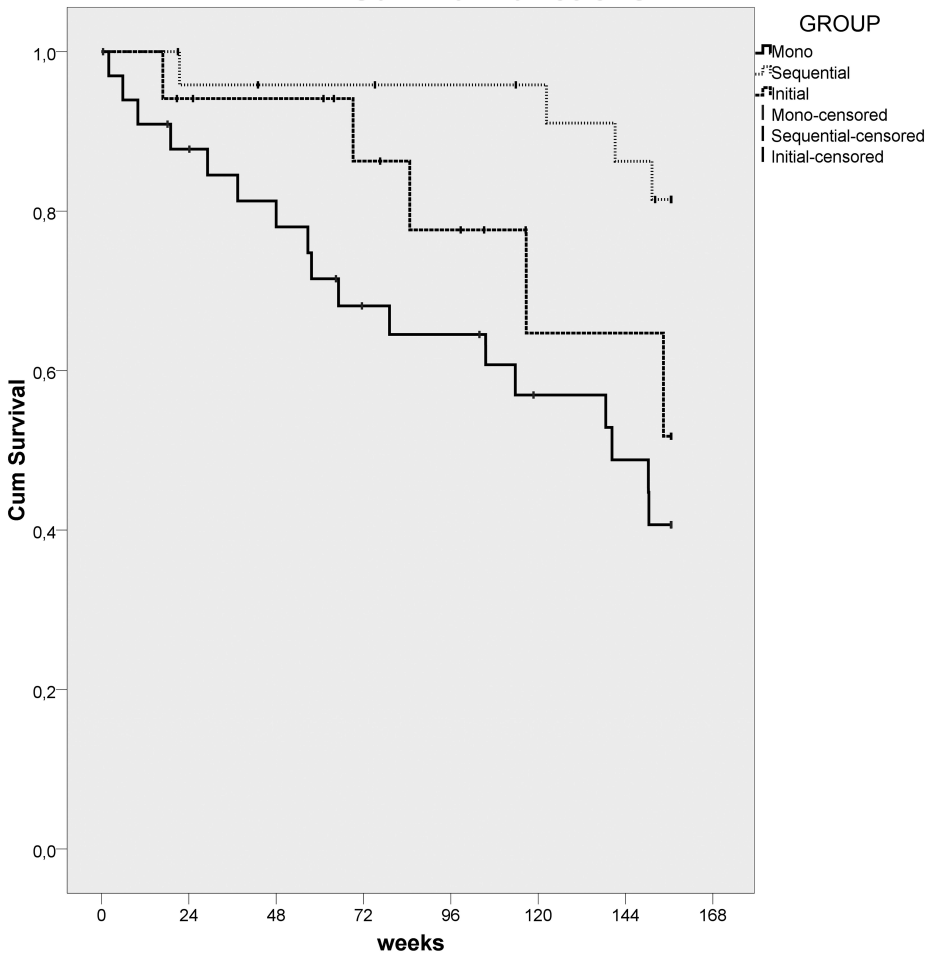

Figure 1. Survival among groups from the diagnosis of pulmonary arterial hypertension. Log-rank ratio p = 0.007.

without ILD, collected retrospectively from 2000 to 2005[20]. In 2009, Condliffe, *et al* reported a 1-, 3-, and 5-year survival of 78%, 47%, and 23%, respectively, in a cohort of 429 CTD-associated PAH cases with 259 SSc-associated PAH, including patients with ILD and almost 30% of patients with combined therapy between 2001 and 2006[21]. The 1- and 3-year survival 86% and 65%, respectively, from the multicentric retrospective study of 78 French patients with SSc-associated PAH without significant ILD, was due to an early diagnosis by a screening program[22]. Survival with first-line bosentan, followed or not by the addition of sildenafil or prostanoids, was 80% and 51% at 1 and 3 years, respectively, in a longterm outcome study published in 2010. That study had 49 SSc-PAH patients, including those with

Table 5. Causes of death.

Variables	Monotherapy	Sequential Combination	Upfront Combination	Global p
ILD	2 (11.8)	0	0	0.564
PAH	7 (41.2)	2 (50)	3 (60)	0.749
PAH + ILD	1 (5.9)	0 (0)	0	0.759
Neoplasm	2 (11.8)	1 (25)	0	0.506
Ischemic myocardiopathy	1 (5.9)	0	0	0.759
Sepsis	1 (5.9)	0	0	0.759
Heart failure	0	1 (25)	1 (20)	0.645
Others	3 (17.6)	0	1 (20)	0.124
Total deaths	17	4	5	

Values are n (%) unless otherwise specified. ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

ILD[23]. The PHAROS cohort started in 2006, with 131 incident SSc-associated PAH patients without ILD, with 56 patients in FC I-II, showed 93% and 75% of survival, at 1 and 3 years, respectively, from PAH diagnosis, with 90% of patients receiving monotherapy[24]. Finally, the contemporary REVEAL registry[25] with 2749 PAH patients without significant ILD, including 504 SSc patients, showed a 5-year survival of 39.6% in incident subjects versus 46.2% in prevalent ones.

In our study, which includes patients mainly diagnosed from 2002 to 2016, 1-, 3-, and 5-year survival with monotherapy was 78%, 40.7%, and 31.6%, respectively. Results are difficult to compare, but our survival rates could have been worse than others because most studies not only analyze survival with monotherapy but include a variable percentage of sequential combination at reassessment, and because of the inclusion of moderate ILD in our study.

Interestingly, studies evaluating sequential combination therapy showed similar results to ours in survival at 1, 3, and 5 years (95.8%, 81.5%, and 56.5%, respectively). In 2005, Hoeper, *et al* analyzed overall survival in an uncontrolled prospective study with goal-oriented therapy in 123 patients with PAH (72% IPAH, 12% CTD-PAH) who started taking bosentan and added sildenafil if monotherapy failed. They had a 1-, 2-, and 3-year survival of 93.3%, 88.3%, and 83.9%, respectively[26]. Our study included only patients with SSc-PAH, who are known to have a worse prognosis, so our results could be interpreted as better outcomes. A metaanalysis by Fox, *et al* in 2011 concluded that combination therapy improved 6-min walk distance but did not decrease mortality, hospital admissions due to PAH, and the need for escalation therapy[27]. In the SERAPHIN study published in 2013, which included 742 PAH patients (30.5% CTD-PAH), macitentan significantly reduced a combined endpoint of morbidity and mortality, also in patients with background therapy with PDE5 inhibitors (60% of the sample), indirectly showing that a combination of ERA and PDE5 inhibitors resulted in better outcomes than monotherapy[28]. In 2015, Dardi, *et al* conducted a retrospective study with 195 patients with sequential combination with sildenafil and bosentan[29], with survival rates at 1, 3, and 5 years similar to ours (91%, 69%, 59%, respectively) but including only 29 CTD-PAH with a worse survival in this subgroup. On the other hand, COMPASS-2 failed to demonstrate superiority of sequential combination therapy with sildenafil and bosentan in 334 patients (88 with CTD-PAH) in delaying time until the first morbidity or mortality event[30]. The metaanalysis of Lajoie, *et al*[31] in 2016 showed lower risk of clinical worsening with combination therapy with RR 0.65 (95% CI 0.58–0.72) and the Fox, *et al* metaanalysis found a reduction of 38% in clinical worsening but without reduction in mortality[32]. Other combination sequential therapies including prostacyclins[33] and soluble guanylate-cyclase stimulators, and triple combination therapy[34] have shown promising outcomes.

Regarding upfront combination therapy, in 2004[35] the BREATHE-2 study compared epoprostenol plus bosentan versus epoprostenol plus placebo, observing a nonsignificant decrease in total pulmonary resistance in the combination group, including only 5 patients with SSc-associated PAH. In 2016, the AMBITION trial[18] demonstrated a reduction of 50% in a morbidity and mortality endpoint with ambrisentan plus tadalafil in 500 Group 1 patients with PAH. In the posthoc analysis of 187 CTD-PAH patients, a reduction of 56% in morbidity and mortality was found in the 118 SSc-associated PAH subset[19].

In our study, upfront combination therapy showed better results than monotherapy in mortality alone but did not reach statistical significance.

The inclusion of patients with moderate ILD has to be taken into account. In the metaanalysis of Lefèvre *et al*[36], survival for isolated PAH at 1, 2, and 3 years was 82%, 67%, and 56%, respectively, and for PAH-related ILD (defined as significant ILD in HRCT plus FVC or TLC around 60–70%, or functional tests alone with FVC or TLC < 60–70%) survival was 75%, 48%, and 35%, respectively. It is important to point out that our study population had a remarkable percentage of ILD, as shown before, mainly

moderate with FVC > 60%, so we could compare our cohort with the isolated SSc-PAH. Even so, better survival was found in the combination group, which was the one with a higher percentage of ILD, although it was not statistically significant. This supports the assertion that patients with SSc-PAH benefit from combination therapy compared to monotherapy, even with a mild to moderate degree of ILD. In fact, another study that focused on transplant-free survival in patients with SSc-associated PAH and ILD has already suggested treating that particular group of patients aggressively with prostanoids, even with significant ILD, because they were a protective factor that improved survival[37].

Therefore, our study results suggest that combination therapy is superior to monotherapy regarding survival. Appreciably, PAH guidelines have included both upfront and sequential combination therapy as first-line treatment, some of them with grade of recommendation and evidence IB[17]. In view of this evidence, which is also supported by our own study, we agree that combined therapy should be used as an initial therapeutic option in the group of SSc patients with PAH.

Independent risk factors for mortality in SSc-related PAH have been widely described[38,39,40,41,42]. In our study, the only independent risk factors of mortality were the prescribed treatment regimen and the FC. In multivariate analysis, sequential combination therapy was a longterm protective factor when compared to monotherapy, with a significant decrease of 89% in mortality. Of major interest, upfront combination therapy also showed a decrease in mortality of 32% but did not reach statistical significance. These findings did not confirm the idea that initiating upfront combination therapy should give better results than escalating therapy, because different pathways are attacked earlier and their effects may mount. The possible explanation is that our sample size under upfront combination therapy was relatively small and most patients had different baseline characteristics that suggested greater severity, some of them statistically significant, such as higher mPAP, and a tendency to a worse FVC, worse DLCO and ratio FVC/DLCO, higher systolic pulmonary arterial pressure (sPAP) by echocardiography, higher TRV, lower tricuspid annular plane systolic excursion, and higher percentage of pericardial effusion.

Other studies included different risk factors in their analyses. We could not analyze all of them given the features of our study, based on a retrospective database in which all variables were predetermined so that we could not add new variables not registered previously in the database. Thus, genetic risk factors associated with poor prognosis were not analyzed in our study because no genetic tests are included in our database. In contrast to other studies[42], PAP, either by echocardiogram or RHC, was not a risk factor in our study, neither in the univariate nor multivariate analysis. In the previous subgroup analysis of functional, echocardiograph, and hemodynamic variables, sPAP was not statistically different between groups, although there were differences and the mPAP was statistically significantly worse in the upfront combination group (perhaps as a reflection of more severe illness). In the risk factor analysis, sPAP showed a trend of higher mortality risk (HR 1.43, 95% CI 0.94–2.17; p = 0.095) but it was not significant, and mPAP showed no higher risk. Further, we checked only changes of > 10 mmHg as a risk factor, and the range of PAP in our patients was narrower. Also, the size of the sample could have been a reason for the lack of statistical significance. In addition, time between SSc onset and diagnosis of PAH was not an independent risk factor in our study, as the univariate Cox regression results show (HR 1.03, 95% CI 0.99–1.0; p = 0.073). In accord with other studies[42], we found that none of these were risk factors for mortality: sex, disease subset, right atrial pressure, or change in DLCO or FVC.

The most important strength of our study is that the investigation focused only on the specific group of patients with SSc-related PAH, and evaluated longterm mortality as a single endpoint instead of a combined endpoint of morbidity and mortality.

Our study has several limitations. First, the retrospective design instead of a controlled trial allows us to reach only general conclusions. Second, the study sample size, shorter than other PAH studies focused on IPAH, may have limited statistical significance of analyzed prognostic factors. On the other hand, the study sample is relevant enough and representative on our national level to assess longterm mortality in the particular patients with SSc-associated PAH.

Our study not only confirmed the superiority of combined therapy versus monotherapy in reducing longterm mortality rates in our Spanish nationwide cohort of patients with SSc-PAH, but also reaffirmed the better survival of the group of patients treated with sequential combination therapy, even with a mild to moderate degree of ILD. Further, our results also suggest that upfront combination therapy might improve survival as well, without statistical confirmation due to study limitations. Thus, further studies are needed to evaluate the exact role of upfront combination compared to sequential combination, because prognosis of SSc-PAH still remains fatal.

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APPENDIX 1.

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