TITLE

LONG-TERM EFFICACY AND SAFETY OF MONOTHERAPY VERSUS COMBINATION THERAPY IN SYSTEMIC SCLEROSIS-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION: A retrospective cohort study from the nationwide Spanish Scleroderma Registry (RESCLE)

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RUNNING HEAD

Monotherapy versus combination

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 efficacy of monotherapy vs. combination therapy in Systemic Sclerosis (SSc)-associated PAH patients.

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

Results: 76 patients (4.2%) out of 1817 had SSc-related PAH. 34 patients (45%) were receiving monotherapy [ERA (22, 29%) or PDE5 inhibitors (12, 16%)], 25 (33%) sequential combination, and 17 (22%) upfront combination. A lower FVC/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 mPAP 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 independent predictors of mortality. Sequential combination was found an independent protective factor [HR=0.11 (95%CI 0.03-0.51), p=0.004], while upfront combination 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% vs. 95.8% vs. 94.1% at 1 year, 40.7% vs. 81.5% vs. 51.8% at 3 years and 31.6% vs. 56.5% vs. 34.5% at 5 years (p=0.007). Side effects were not significantly different among groups.

Conclusions: Combination sequential therapy improved survival in our cohort.

Abbreviations: SSc, systemic sclerosis; CTD, connective tissue disease; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis; IPAH/FPAH, idiopathic or familiar pulmonary arterial hypertension; WHO, World Health Organization; ERA, endothelin receptor antagonist; PDE5, phosphodiesterase-5; RESCLE, Spanish Scleroderma Registry; GEAS, Autoimmune Diseases Working Group; SEMI, Spanish Society of Internal Medicine; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; SD, standard deviation; ANOVA, analysis of variance; FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; HR, hazard ratio; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal pro b-type natriuretic peptide; TRV, tricuspid regurgitation velocity; sPAP, systolic pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; FEV1, forced expiratory volume during the first second; ATA, anti-topoisomerase I antibody; ACA, anti-centromere antibody; anti-RNA pol III, anti-RNA polymerase III antibody; Anti-RNP, anti-ribonucleoprotein antibody.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease (CTD) of unknown origin. PAH is one of the most devastating complications, with a prevalence of 12-13%[1-5]. Left untreated, it leads to right ventricular failure and death. Its prognosis is worse than idiopathic/familial PAH (IPAH/FPAH) and other CTD-related PAH, being one of the main SSc-related causes of death[6-8]. SSc-related PAH survival has improved since the 80's due to better disease knowledge, screening programmes and emerging therapies[9-13]. However, mortality is still high.

Monotherapy remains an option for PAH treatment[14-16] recommended in guidelines[17] as first-line therapy for World Health Organization (WHO) 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 (IB) is the same as monotherapy, recent reports, including the AMBITION trial[18] and its post-hoc analysis[19] focused on CTD-PAH patients, suggest combination therapy as a better option to treat PAH, demonstrating its superiority in terms of morbimortality.

Our study was designed to evaluate the long-term 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 impact 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 (SEMI), which includes patients with SSc who fulfilled the 2013 ACR/EULAR criteria and/or the modified criteria proposed by LeRoy and Medsger in 1988 to avoid the possible missing of patients with scleroderma sine scleroderma or limited cutaneous systemic sclerosis who could not fulfill the 2013 ACR criteria. Data were collected retrospectively until 2006 and prospectively onwards. 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) as well (ref. PR126/13).

Inclusion criteria were SSc-patients aged 18 years or more, with a diagnosis of PAH by right heart catheterization (RHC) with a mean pulmonary arterial pressure (mPAP) of ≥25mmHg, a pulmonary capillary wedge pressure (PCWP) of ≤15mmHg and a pulmonary vascular resistance (PVR) of >3 Wood units, without ILD or with moderate ILD defined by FVC >60% and not significant interstitial pattern on 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 approval.

The patient population was split up in three groups according to treatment regimen: a) *monotherapy* with ARE or PDE5 inhibitors; b) *sequential combination therapy*, defined by ≥12 weeks between initiation of first and second drug; c) *upfront combination therapy*, defined by <12 weeks between first and second drug. Cutting-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 in order to decide effectiveness of treatment or whether escalating treatment is needed[14-16]. Furthermore, in the recently published 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, NYHA FC, visceral involvement, antibody profile, pulmonary functional tests (PFT), echocardiography measures and hemodynamic parameters 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 three 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 ± standard deviation (SD) for quantitative variables. Categorical variables were analyzed using Chi-square test and quantitative variables were analyzed with the analysis of variance (ANOVA). The Bonferroni's correction was applied for multiple comparisons among categorical variables. A univariate and multivariate Cox's proportional hazards model was performed in order 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 follow-up was reported.

RESULTS

Seventy-six patients with SSc-related PAH treated with ARE, PDE5 inhibitors or both were identified among 1817 SSc-patients of the RESCLE database, diagnosed between 2002 to 2016, except form one 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: current smokers 1 patient (3%) vs. 2 (8.3%) vs. 1 (6.7%) (p=0.674); former smokers 6 patients (18%) vs. 4 (17%) vs. 4 (27%) (p=0.722); and never smokers 26 patients (79%) vs. 18 (75%) vs. 10 (67%), p=0.668. The age at onset of SSc was around 50 years-old (48.5±14.9 years-old vs. 51.7±15 vs. 48±15.8, p=0.694) and the age at diagnosis of SSc close to 60 years-old (58.9±15.6 years-old vs. 59.6±14.9 vs. 57.7±13.4, 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 without reaching statistical significance (11.8±12.6 years vs. 5.8±9.8 vs. 10.3±17.2, p=0.277). The mean follow-up from the first symptom of SSc was 20.9±12.5 years vs. 16.9±10.3 vs. 17.7±15.9 (p=0.511) and the mean follow-up from the diagnosis of SSc was 9.8±8.3 years vs. 9.7±7.4 vs. 8.5±7.8 (p=0.851) for monotherapy vs. sequential combination therapy vs. upfront combination therapy respectively. Regarding to PAH, the time from first SSc symptom until definitive PAH diagnosis was 19.5±12.8 years vs. 11.6±11.7 vs. 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%) vs. 16 (64%) vs. 9 (56%) (p=0.835), dcSSc in 6 patients (18%) vs. 5 (20%) vs. 4 (25%) (p=0.832) and *sine scleroderma* in 6 patients (18%) vs.

4 (16%) vs. 3 (19%) (p=0.973) for monotherapy, sequential combination and upfront combination therapy respectively.

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's correction confirmed statistical significance in pericardial involvement between upfront combination vs. monotherapy and sequential combination. Although it did not reach statistical significance, the percentage of ILD was different between groups, with 58% vs. 80% vs. 76.4% for monotherapy, sequential combination and upfront therapy respectively. Of those, the majority of patients had moderate ILD as defined earlier, with 55% vs. 70% vs. 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 %forced vital capacity/%diffusing capacity of the lung for carbon monoxide ratio (%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±8.7mmHg vs. 40.8±8.8 vs. 46±15.9, p=0.026). The Bonferroni's correction confirmed statistical significance in mPAP between upfront combination vs. monotherapy.

Risk factors of mortality

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

After a multivariate analysis, the prescribed treatment regimen (p=0.017) and FC at baseline (p=0.007) were found independent predictors for long-term mortality (table 3). Taking monotherapy as reference treatment, sequential combination therapy was found to be a protective factor [HR=0.11 (95%CI 0.03-0.51), p=0.004] and upfront combination therapy showed a tendency of protection, without reaching statistical significance [HR=0.68 (95%CI 0.23-1.97), p=0.476].

Survival and causes of death among groups

Long-term survival rates from diagnosis of SSc-related PAH among groups for monotherapy, sequential combination and upfront combination were, respectively, as follows: 78% vs. 95.8% vs. 94.1% at 1 year, 40.7% vs. 81.5% vs. 51.8% at 3 years and 31.6% vs. 56.5% vs. 34.5% at 5 years (log-rank test p=0.007). Data of surviuval 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 follow-up. The causes of mortality among groups are shown in table 5. Death secondary to SSc-related PAH was the main cause of death in all groups [8 patients (47.1%) vs. 2 (50%) vs. 3 (60%), p=0.749].

Side effects among groups

Side effects were not significantly different among groups [10 patients (29%) vs. 8(32%) vs. 2(12%), p=0.295]. Most frequent side effects were as follows: edema, anemia, hepatotoxicity, arterial hypotension and headache attributed to AREs and rash, headache and hepatotoxicity due to PDE5 inhibitors.

DISCUSSION

In our study, we evaluated long-term efficacy and safety of monotherapy versus combination therapy for PAH in a large Spanish SSc-patient cohort. Results showed better long-term survival rates for the overall combination therapy groups. Moreover, sequential combination therapy showed superiority against monotherapy as a long-term 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 in regard to NHYA FC, PAH specific regimens used, inclusion of incident or prevalent patients and inclusion of some degree of ILD. Mukerjee *et al.*[20] 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%. Williams *et al.* demonstrated better survival since introduction of Bosentan comparing two cohorts of SSc-associated PAH patients in FC III-IV, without significant ILD, showing 1 and 2 year survival of 68% and 47% in the

historical cohort (before 2002) and 81% and 71% in the contemporary cohort[12]. Fisher *et al.* reported a 1 and 3 year-survival of 87.7% and 48.9% in 50 patients with SSc-associated PAH without ILD, collected retrospectively from 2000 to 2005[21]. In 2009, Condliffe *et al.* reported a 1, 3 and 5 year survival of 78%, 47% and 23% in a cohort of 429 CTD-associated PAH with 259 SSc-associated PAH, including patients with ILD and almost 30% of patients with combined therapy between 2001 and 2006[22]. The 1 and 3-year survival 86% and 65% 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[23]. Survival with first line bosentan, followed or not by the addition of sildenafil or prostanoids, was 80% and 51% at 1 and 3 years in a long term outcome study published in 2010, which included 49 SSc-PAH patients, including those with ILD[24]. 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 from PAH diagnosis, with 90% of patients receiving monotherapy[25]. Finally, in the contemporary REVEAL registry[26] with 2749 PAH patients without significant ILD, including 504 SSc patients, showed a 5-year survival of 39.6% in incident subjects vs. 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%. Results are difficult to compare, but our survival could have been worse than others since 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.

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%). In 2005, Hoeper *et al.* analyzed overall survival in an uncontrolled prospective study with goal-oriented therapy in 123 PAH patients (72% IPAH, 12%, CTD-PAH) that started bosentan and added sildenafil if monotherapy failed, a 1, 2 and 3 year survival of 93.3%, 88.3% and 83.9%[27]. Our study only included SSc-PAH patients, which are known to have a worse prognosis, so our results could be interpreted as better outcomes. Fox *et al.* meta-analysis in 2011 concluded that combination therapy improved 6-minute walk distance (6MWD) but did not decrease mortality, hospital admissions due to PAH, and the need of escalation therapy[28]. In the SERAPHIN study published in 2013, which included 742 PAH patients with 30.5% of CTD-PAH, macitentan significantly reduced a combined endpoint of morbimortality, also in patients with background therapy with PDE5 inhibitors (60% of the sample), indirectly showing that combination of ERA and PDE5 inhibitors had better outcomes than monotherapy[29]. In 2015, Dardi *et al.* conducted a retrospective study with 195 patients with sequential combination with sildenafil and bosentan[30], with survival rates at 1, 3 and 5 years similar to ours (91%, 69%, 59%) 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 with sildenafil and bosentan, in 334 patients (88 with CTD-PAH) in delaying time until the first morbimortality event. The meta-analysis of Lajoie *et al.*[32] in 2016 showed lower risk of clinical worsening with combination therapy with RR 0.65 (95%CI 0.58-0.72) and Fox *et al.*[33] meta-analysis found a reduction of 38% in clinical worsening but without reduction in mortality. Other combination sequential therapies including

prostacyclins[34] and soluble guanylate-cyclase stimulators and triple combination therapy[35] have shown promising outcomes.

Regarding upfront combination therapy, in 2004[36] the BREATHE-2 study compared epoprostenol plus bosentan vs. epoprostenol plus placebo, observing a non-significant decrease in total pulmonary resistance in the combination group, including only 5 SSc-associated PAH patients. In 2016, the AMBITON trial demonstrated a reduction of 50% in a morbimortality endpoint with ambrisentan plus tadalafil in 500 group1-PAH patients. In the post-hoc analysis of 187 CT-PAH patients, a reduction of 56% in morbimortality was found in the 118 SSc-associated PAH subset[19].

In our study, upfront combination 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 in account. In the meta-analysis of Lefèvre[37], 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 and even so, better survival was found in the combination group, which was the one with higher percentage of ILD although not statistically significant. This supports the fact that SSc-PAH patients benefit from combination therapy compared to monotherapy, even with a mild to moderate degree of ILD. In fact, another study

that focused in 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, as they were a protective factor that improved survival[38].

Therefore, our study results suggest that combination therapy is superior to monotherapy in terms of survival. Appreciably, PAH guidelines have recently 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 the recently reported evidence, also supported by our own study, we agree that combined therapy should be used as initial therapeutic option in the group of SSc-patients with PAH.

Independent risk factors for mortality in SSc-related PAH have been widely described[39-42]. 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 long-term 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 suggest 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 (TAPSE) and higher percentage of pericardial effusion.

Other studies included different risk factors in their analyses. We could not analyze all of them given the nature of our study, based in a retrospective database in which all parameters were predetermined so that we could not add new parameters 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[43], PAP, either by echocardiogram or right heart catheterization was not a risk factor in our study, neither in the univariate nor multivariate analysis. In the previous subgroups analysis of functional, echocardiograph and hemodynamic parameters, 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 (0.94-2.17); p=0.095)] but not significant and mPAP showed no higher risk. Furthermore, we only checked changes of more than 10mmHg as a risk factor and the range of PAP in our patients were narrower. Also, the size of the sample could have been a reason for the lack of statistical significance. Time between SSc onset and diagnosis of PAH was neither an independent risk factor in our study, as the univariate Cox's regression results show HR=1.03 (95% CI; 0.99-1.0), p=0.073. Accordingly to other studies[43], we did find neither gender, disease subset, right atrial pressure nor change in DLCO or FVC as risk factors for mortality.

In our opinion, the most important strength of the present study is the fact that the investigation only focused on the specific group of SSc-related PAH patients, and evaluated long-term mortality as a single endpoint instead of a combined endpoint of morbidity and mortality.

Our study has several limitations. Firstly, the retrospective design instead of a controlled trial allows us to reach only general conclusions. Secondly, 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 long term-mortality in the particular SSc-associated PAH patients.

In conclusion, our study not only confirmed the superiority of combined therapy versus monotherapy on reducing long-term mortality rates in our Spanish nationwide cohort of SSc-PAH patients, 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. Furthermore, our results also suggest that upfront combination 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, since prognosis of SSc-PAH still remains fatal.

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FIGURE LEGENDS

Figure 1. Survival among groups from the diagnosis of PAH. Log Rank ratio p-value=0.007.

APPENDIX

RESCLE Registry members:

Callejas Moraga E, Carbonell C, Chamorro AJ, Colunga D, Corbella X, Espinosa G, Estévez M, Fernández de la Puebla RA, Fonollosa V, Freire M, Gracia Tello B, Guillén del Castillo A, Iniesta N, Lorenzo R, Madroñero AB, Marín Ballvé A, Ortego-Centeno N, Perales I, Pestaña-Fernández M, Pla Salas X, Pons Martín del Campo I, Rodríguez Carballeira M, Rubio-Rivas M, Ruiz Muñoz M, Salvador G, Segovia P, Simeón CP, Tarí E, Todolí JA, Tolosa C, Trapiella L, Vargas Hitos JA.

Table 1. General features among groups.

	Monotherapy	Sequential combination	Upfront combination	Global p-value	Monotherapy vs. sequential p-value	Monotherapy vs. upfront p-value
Patients	34	25	17			
Peripheral vascular involvement n (%)						
Raynaud's 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
Acrosteolysis	1 (5.3)	3 (23)	0	0.162	0.279	1.000
Musculoskeletal involvement n (%)	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 n (%)	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 n (%)	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 n (%)	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 n (%)	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 n (%)	6 (18)	5 (20)	4 (24)	0.883	1.000	0.714
Capillaroscopy n (%)	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 n (%)						
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-RNA pol 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

ILD: interstitial lung disease; ATA: Anti-topoisomerase I antibody; ACA: Anti-centromere antibody; Anti-RNA pol III: Anti-RNA polymerase III antibody; Anti-RNP: Anti-ribonucleoprotein antibody.

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

	Monotherapy	Sequential combination	Upfront combination	Global p-value	Monotherapy vs. sequential p-value	Monotherapy vs. upfront p-value
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 (%mean and SD)	67.6±19.6	71.7±22.6	59.7±23.8	0,500	0.661	0.403
DLco (%mean and SD)	25.3±13.5	43.6±18.6	38.1±16.9	0.183	0.080	0.218
FEV1 (%mean and SD)	63.4±6.8	63.3±6.8	64.7±6.7	0.894	0.988	0.664
FVC/DLco (mean and SD)	2.9±1.1	1.8±0.4	2.3±0.8	0.085	0.043	0.365
sPAP by echocardiography						
mmHg (mean and SD)	62.2±21.5	64.0±14.3	79.3±31.9	0.260	0.834	0.152
TRV m/s (mean and SD)	3.7±0.7	3.7±0.6	3.9±1.0	0.798	0.973	0.532
TAPSE mm (mean and SD)	19.5±1.3	20.5±2.1	13.1±9.6	0.319	0.495	0.275
Pericardial effusion n (%)	3 (19)	2 (22)	4 (50)	0.248	1.000	0.167
Right ventricular dilation n (%)	7 (44)	5 (56)	4 (67)	0.608	0.688	0.635
mPAP mmHg (mean and SD)	37.2±8.7	40.8±8.8	46.0±15.9	0.026	0.120	0,046
PCWP mmHg (mean and SD)	12.8±6.2	11.1±4.1	14.2±5.0	0.254	0.303	0.467
Cardiac output litres/minute						
(mean and SD)	4.2±1.3	4.3±1.7	4.2±1.7	0.963	0.775	0.898
PVR Wood units (mean and SD)	8.2±5.9	8.1±3.8	8.3±4.9	0.994	0.947	0.966

PFT: pulmonary functional tests; FVC: forced vital capacity; SD: standard deviation; DLco: diffusing capacity of the lung for carbon monoxide; 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 pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

Table 3. Risk factors associated with mortality.

	Univariate Analysis HR (95%CI)	p-value	Multivariate analysis HR (95%CI)	p-value
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-year 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.)	-
Seqüential 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 (1.89-24750897)	0.030	-	
sPAP per ECO per 10-mmHg change	1.43 (0.94-2.17)	0.095	-	
VRT 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	-	

HR: hazard ratio; DcSSc: diffuse cutaneous Systemic sclerosis; FVC: forced vital capacity; DLco: diffusing capacity of the lung for carbon monoxide; sPAP: systolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; RHC: right heart catheterization; TRV: tricuspid regurgitation velocity; TAPSE: tricuspid annular plane systolic excursion; RAP: right atrial pressure.

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

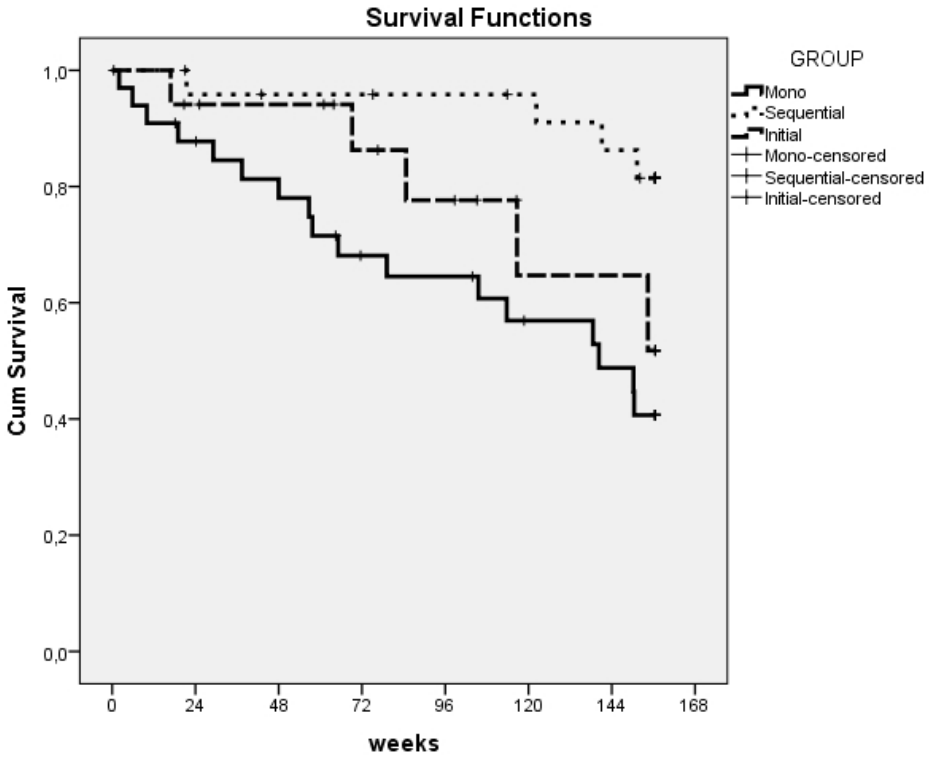
Survival	4 weeks	26 weeks	52 weeks	04 weeks	156 weeks
Monotherapy	0.970	0.878	0.780	0.645	0.407
Sequential combined therapy	1.000	0.958	0.958	0.958	0.815
Upfront combined therapy	1.000	0.941	0.941	0.776	0.518

Patients on 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

Table 5. Causes of death.

	Monotherapy	Sequential combination	Upfront combination	Global p-value
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
Ischaemic 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	

ILD: Interstitial lung disease; PAH: pulmonary arterial hypertension.



Survival among groups from the diagnosis of PAH. Log Rank ratio p-value=0.007.

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