

Association Between Initial Oral Therapy and Outcomes in Systemic Sclerosis–Related Pulmonary Arterial Hypertension

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Objective. To compare time to clinical worsening (TTCW) based on initial oral therapy for pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc)–related PAH.

Methods. Using data from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry (a multicenter prospective observational study enrolling SSc patients with incident pulmonary hypertension), we selected patients with group 1 PAH (World Health Organization Clinical Classification system) who received initial therapy (for 6 months) with an endothelin receptor antagonist (ERA), a phosphodiesterase 5 (PDE5) inhibitor, or a combination of these 2 agents (ERA/PDE5 inhibitor). The main outcome was TTCW, defined as the first occurrence of death, PAH-related hospitalization, lung transplantation, initiation of parenteral prostacyclin treatment, or worsening symptoms.

Results. Ninety-eight patients (24 in the ERA group, 59 in the PDE5 inhibitor group, and 15 in the ERA/PDE5 inhibitor group) were included. No significant differences in the baseline characteristics of the patients were observed. TTCW was significantly worse in patients in the ERA group compared with those in the PDE5 inhibitor group or the ERA/PDE5 inhibitor group. Ten patients (41.6%) in the ERA group died during the 3-year observation period, compared with 4 patients (6.8%) in the PDE5 inhibitor group and 1 patient (6.7%) in the ERA/PDE5 inhibitor group. Baseline factors that were independently associated with a shorter TTCW were initial treatment with an ERA (hazard ratio [HR] 2.63 [$P = 0.009$]), lower diffusing capacity for carbon monoxide (HR 0.69 per 10% of predicted change [$P = 0.04$]), and higher pulmonary vascular resistance (HR 1.10 per Wood unit change [$P = 0.007$]).

Conclusion. Compared with initial treatment with a PDE5 inhibitor or combination therapy with an ERA and a PDE5 inhibitor, initial therapy with an ERA

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in patients with SSc-related PAH was associated with significantly worse TTCW, even after adjustment for commonly accepted prognostic factors. Further study into the optimal initial oral therapy for patients with SSc-related PAH is needed.

Systemic sclerosis (SSc; scleroderma) is a multiorgan heterogeneous disorder characterized by endothelial dysfunction and vasculopathy, inflammation, fibroblast dysregulation, and abnormal immune system functioning. Hemodynamically confirmed pulmonary arterial hypertension (PAH) complicates SSc, with an estimated prevalence of 8–12% (1), and is a leading cause of death in this patient population. In addition, PAH accounts for up to 30% of premature deaths in patients with SSc (2). Despite advances in treatment, patients with SSc-related PAH still have a 3-fold higher risk of death compared with patients with idiopathic PAH (3). Furthermore, the response to therapy, as assessed by changes in functional capacity and survival, seems to be less robust in patients with SSc-related PAH compared with that in patients with other forms of PAH (4,5). The optimal treatment strategy for patients with SSc-related PAH remains to be defined.

Drug studies in PAH have included heterogeneous patient populations, with a mix of patients with idiopathic PAH, patients with heritable PAH, patients with SSc-related PAH, and those with other associated causes of group 1 pulmonary hypertension (PH), as defined by the World Health Organization (6). Few subgroup analyses have focused on patients with SSc (7–11). Although more recent studies have included patients receiving background therapy, there is a relative lack of head-to-head comparisons of oral medications used for the initial treatment of PAH. Descriptions of long-term clinical experience with the medications used to treat PAH outside of carefully controlled randomized trials are also needed.

Using data from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry of patients with SSc-related PAH, we performed a retrospective cohort study to examine whether the choice of initial oral medication is associated with differential outcomes. We hypothesized that there would be no difference in time to clinical worsening (TTCW) or survival in patients who initially started treatment with an endothelin receptor antagonist (ERA) compared with those who started treatment with a phosphodiesterase 5 (PDE5) inhibitor. Additionally, we hypothesized that, given the potential for synergistic effects, clinical outcomes would be improved when patients were started on both an ERA and a PDE5 inhibitor compared with either agent given as initial monotherapy.

PATIENTS AND METHODS

The PHAROS registry is a North American multicenter, prospective, observational study established in 2006, enrolling SSc patients at high risk of developing PH and those with incident PH (12). This registry was set up to understand the natural history of PH development in SSc and to observe the course of disease progression in those with incident PH. The current analysis is a retrospective cohort study utilizing data from the prospective PHAROS registry. This study was approved by the Tulane University Institutional Review Board (no. 685867). See Appendix A for the names and locations of the PHAROS investigators.

Patient selection and definitions. Of the 178 patients who were judged by the PHAROS investigators to have incident group 1 PAH at the time of the data download (performed on May 14, 2014), 98 were included in this analysis (Figure 1). Patients were included if they had group 1 PAH (13) based on right heart catheterization (RHC) performed within 6 months prior to enrollment in the registry. This time point for the landmark analysis (14) was chosen a priori. Patients were excluded if they had a pulmonary artery wedge pressure (PAWP) of >15 mm Hg (to exclude those with PH due to left heart disease) or a forced vital capacity and total lung capacity of <65% of predicted and moderate/severe fibrosis on computed tomography (to exclude those with PH predominantly from interstitial lung disease).

The patients who were included were required to have received initial therapy (for 6 months) exclusively with either an ERA, a PDE5 inhibitor, or the combination of these 2 agents (ERA/PDE5 inhibitor). Patients who were initially treated with prostanoids were excluded. These exclusions account for the difference between the number of patients in the registry with group 1 PAH (n = 178) and the number of patients included in this analysis (n = 98).

In an attempt to control for therapies that were added after the initial 6-month period, “time on initial therapy” (with ERA, PDE5 inhibitor, or ERA/PDE5 inhibitor) was calculated. For example, if a patient was started on an ERA and a PDE5 inhibitor was added 12 months later, time on initial therapy would be 1 year. To account for any delay in the initiation of therapy, time from diagnostic RHC to the start of treatment (medication) was compared between groups. To avoid immortal time bias, the starting point for all analyses was the date when the initial therapy was started. Disease duration was calculated based on the period of time from the onset of Raynaud’s phenomenon to enrollment in the registry. The SSc subtype (limited versus diffuse) was assigned based on standard definitions (15).

Outcomes. The main outcome was TTCW over a 3-year period. TTCW was defined as the first occurrence of all-cause death, PAH-related hospitalization, lung transplantation, initiation of parenteral prostanoid therapy, or worsening of symptoms over 3 years of followup (8). Worsening of symptoms was defined as a decrease of >15% in the 6-minute walk distance *and* worsening of the New York Heart Association (NYHA) functional class (16) *and* the addition of a PH-specific medication (8).

Statistical analysis. Continuous baseline variables, as well as time on initial therapy, were compared between the 3 initial treatment groups using one-way analysis of variance with Tukey’s post-test. Categorical variables were compared

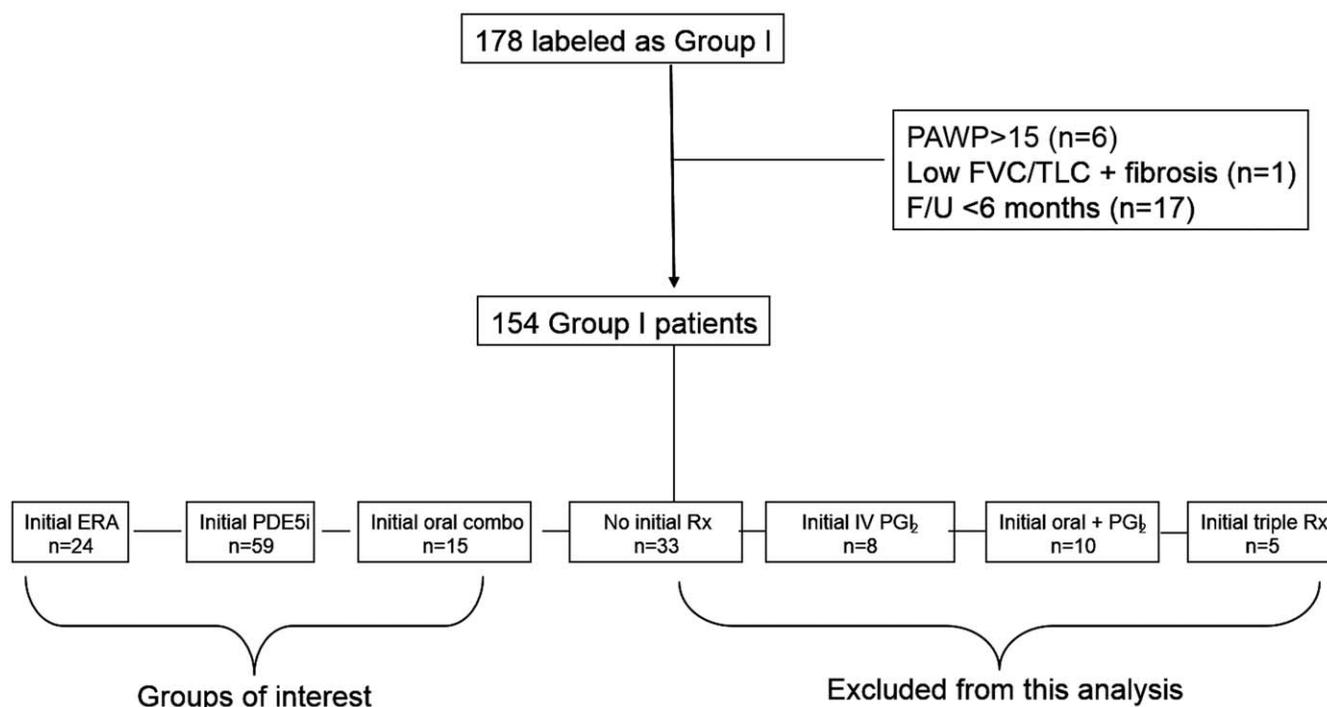


Figure 1. Patient selection. PAWP = pulmonary artery wedge pressure; FVC = forced vital capacity; TLC = total lung capacity; F/U = followup; ERA = endothelin receptor antagonist; PDE5i = phosphodiesterase 5 inhibitor; combo = combination; Rx = treatment; IV = intravenous; PGI₂ = prostaglandin I₂.

using chi-square tests. For TTCW and survival, Kaplan-Meier survival curves were constructed, and log rank analysis was performed to compare outcomes between the 3 groups. Cox proportional hazards regression was used to assess baseline factors associated with TTCW. Examining the proportionality assumptions of the Cox proportional hazards model using both log-log curves and Schoenfeld residuals demonstrated that all assumptions were met. Univariate variables with a *P* value of less than 0.16 were included in the multivariate model (17), and stepwise regression with backward elimination was conducted, with a *P* value threshold for elimination of 0.20. The regression analysis was also repeated by 1) forward selection and 2) sensitivity analysis using a more stringent *P* value threshold (<0.10) along with variables shown in prior SSc-related PAH cohorts to predict outcome. Collinearity between hemodynamic variables was assessed using linear regression models to calculate variance inflation factors, with a variance inflation factor value of >10 indicating that variables were collinear (18). There was no significant collinearity between mean pulmonary artery pressure, cardiac output, and pulmonary vascular resistance (PVR). Statistical analyses were conducted using GraphPad Prism version 5 and Stata version 13. *P* values less than 0.05 were considered significant. For review, see ref. 19.

RESULTS

Patient characteristics. There were no statistically significant differences in the baseline characteristics of the 3 initial therapy groups (Table 1). Of note,

there were no differences between groups in variables known to be associated with disease severity or a poor prognosis, such as the 6-minute walk distance, cardiac output, or NYHA functional class (20–22). There were no significant differences in time on initial therapy between the ERA group (mean ± SD 2.21 ± 1.94 years), the PDE5 inhibitor group (1.98 ± 1.51 years), and the ERA/PDE5 inhibitor group (2.00 ± 1.17 years) (*P* = 0.10). There was no significant difference in the length of time from the diagnostic RHC to the start of therapy (for the ERA group, median 32 days [interquartile range (IQR) –1, 66]; for the PDE5 inhibitor group, median 18 days [IQR 5, 57]; for the ERA/PDE5 inhibitor group, median 1 day [IQR –2, 47]; *P* = 0.65).

In the ERA group, 16 patients were treated with bosentan and 8 with ambrisentan; in the PDE5 inhibitor group, 43 patients were treated with sildenafil and 16 with tadalafil. Patients in the ERA/PDE5 inhibitor group were treated with sildenafil plus bosentan (*n* = 5), tadalafil plus ambrisentan (*n* = 8), or sildenafil plus ambrisentan (*n* = 2). Followup for vital status (alive or dead) was complete in 88% of patients. A description of the medications that were added after the first 6 months of initial therapy in each group is available from the corresponding author.

Table 1. Baseline characteristics of 98 SSc patients with group 1 PAH from the PHAROS registry according to the initial treatment received*

Characteristic	ERA (n = 24)	PDE5 inhibitor (n = 59)	ERA/PDE5 inhibitor (n = 15)
Age, years	61.8 ± 10.3	60.0 ± 11.1	60.3 ± 12.0
Female sex, %	79	83	80
SSc duration, years	10.9 ± 9.8	10.6 ± 9.5	12.4 ± 11.5
Limited cutaneous SSc, %	71	69	93
FVC, % predicted	78.3 ± 19.7	78.6 ± 15.9	86.9 ± 13.0
DLco, % predicted	35.8 ± 16.6	43.9 ± 16.9	48.0 ± 18.5
FVC/DLco ratio	2.0 ± 0.6	2.1 ± 0.8	2.0 ± 0.7
6-minute walk distance, meters	373 ± 80	324 ± 130	355 ± 127
Creatinine, gm/dl	1.05 ± 0.50	1.03 ± 0.81	0.97 ± 0.32
Mean PAP, mm Hg	38.0 ± 9.8	35.6 ± 8.4	39.3 ± 10.7
PAWP, mm Hg	9.3 ± 3.4	10.1 ± 3.1	9.5 ± 2.6
Cardiac output, liters/minute	5.2 ± 2.0	5.1 ± 1.6	5.1 ± 1.8
PVR, Wood units	6.3 ± 3.6	5.8 ± 4.6	7.7 ± 5.5
Pericardial effusion, %	25	35	20
Oxygen use, %	29	32	47
NYHA functional class, %			
1	13	12	13
2	38	39	33
3	50	47	47
4	0	2	7
Time on initial therapy, years	2.21 ± 1.94	1.98 ± 1.51	2.00 ± 1.17
Time from RHC to start of therapy, median (IQR) days	32 (-1, 66)	18 (5, 57)	1 (-2, 47)

* Except where indicated otherwise, values are the mean ± SD. No significant differences were observed. SSc = systemic sclerosis; PAH = pulmonary arterial hypertension; PHAROS = Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase 5; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; NYHA = New York Heart Association; RHC = right heart catheterization; IQR = interquartile range.

Time to clinical worsening. For the TTCW analysis, the total patient-years at risk was 187.6; the mean ± SD time at risk was 2.0 ± 1.0 years. Overall, the

qualifying event for TTCW was death in 8 patients (8%), hospitalization in 14 patients (14%), and initiation of parenteral prostanoid in 8 patients (8%); 68

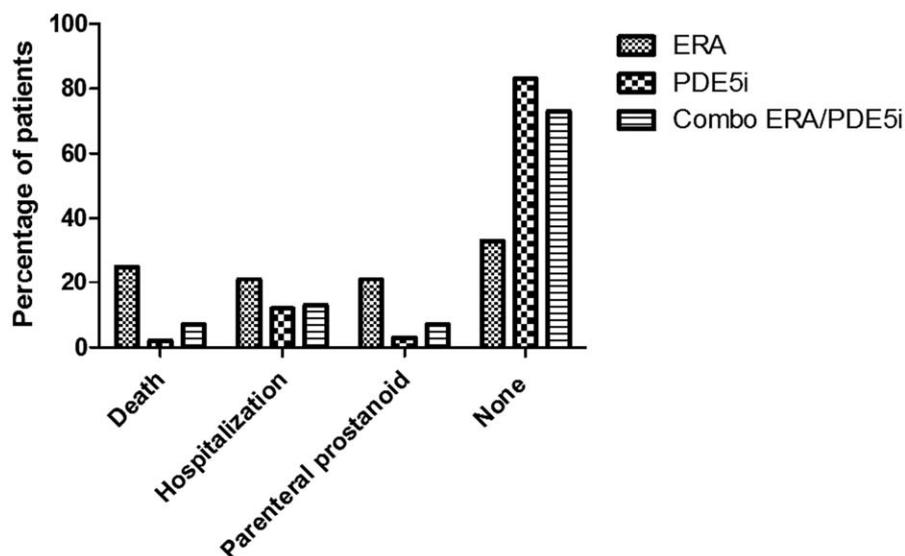
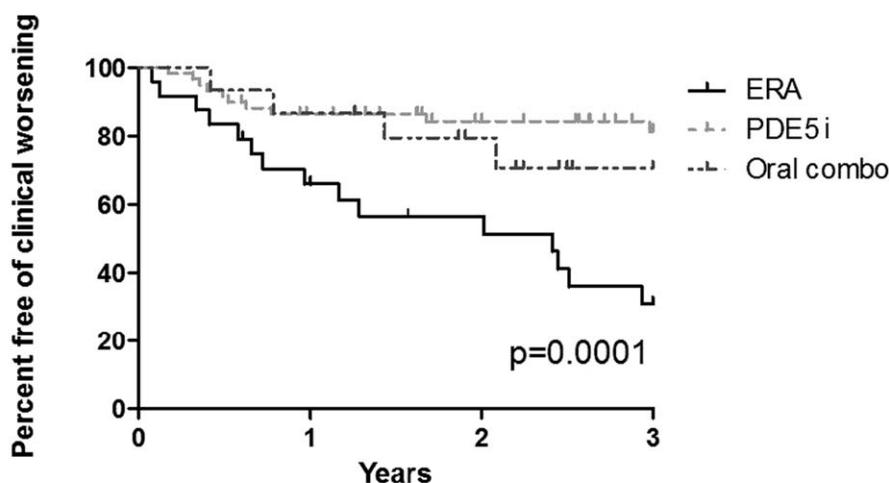


Figure 2. Percentage of patients with qualifying events for time to clinical worsening, stratified by initial oral therapy. No patients had transplantation or worsening symptoms as the qualifying event. See Figure 1 for definitions.



Number at risk

	0	1	2	3
ERA	24	15	12	6
PDE5i	59	49	39	28
Oral combo	15	14	10	3

Figure 3. Kaplan-Meier curves showing time to clinical worsening in patients initially treated with an ERA, patients initially treated with a PDE5 inhibitor, and patients initially treated with a combination of these agents. See Figure 1 for definitions.

patients (69%) did not have a TTCW qualifying event over the 3-year observation period (Figure 2). Ten patients (41.6%) in the ERA group died during the 3-year observation period, compared with 4 patients (6.8%) in the PDE5 inhibitor group and 1 patient (6.7%) in the ERA/PDE5 inhibitor group ($P = 0.004$). Patients initially treated with an ERA had a significantly shorter TTCW ($P = 0.0001$) (Figure 3), with a median

TTCW of 2.4 years. The percentage of patients free of clinical worsening was lower in the ERA group (63.0% at 1 year, 52.3% at 2 years, and 34.8% at 3 years) compared with the PDE5 inhibitor group (85.9%, 83.7%, 80.8%, respectively) or the ERA/PDE5 inhibitor group (85.7%, 77.9%, 68.2%, respectively).

Univariate factors associated with a shorter TTCW were initial treatment with an ERA (compared

Table 2. Univariate factors associated with shorter time to clinical worsening*

Factor	HR	95% CI	P
FVC, per 10% of predicted change	0.92	0.73–1.16	0.48
ERA vs. PDE5 inhibitor	5.00	2.27–11.11	<0.0001†
ERA vs. ERA/PDE5 inhibitor	2.94	0.99–9.09	0.053†
DLco, per 10% of predicted change	0.73	0.54–0.99	0.04†
6-minute walk distance, per 20-meter change	0.99	0.93–1.05	0.65
Mean PAP, per 10-mm Hg change	1.43	0.97–2.10	0.07†
PAWP, per 1-mm Hg change	0.88	0.78–0.98	0.02†
Cardiac output, per 1-liter/minute change	0.77	0.60–0.98	0.03†
PVR, per Wood unit change	1.11	1.05–1.18	0.001†
Age, per 10-year change	1.28	0.9–1.80	0.17
SSc duration, per year change	0.99	0.95–1.03	0.66
Sex, female vs. male	1.05	0.36–3.01	0.93
NYHA functional class	1.26	0.73–2.20	0.41
SSc subtype, limited vs. diffuse	0.91	0.39–2.14	0.84
Time on initial therapy, per 50-day change	0.96	0.92–0.99	0.046†
Time to start of initial medication, per 50-day change	0.98	0.65–1.47	0.92

* HR = hazard ratio; 95% CI = 95% confidence interval; FVC = forced vital capacity; ERA = endothelin receptor antagonist; PDE5 = phosphodiesterase 5; DLco = diffusing capacity for carbon monoxide; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; NYHA = New York Heart Association; SSc = systemic sclerosis.

† Included in the multivariate model.

Table 3. Stepwise backward regression analysis for variables associated with shorter time to clinical worsening*

Variable	HR	95% CI	P
Initial medication, ERA vs. others	2.63	1.28–5.56	0.009
DLco, per 10% of predicted change	0.69	0.49–0.99	0.04
PVR, per Wood unit change	1.10	1.03–1.18	0.007
PAWP, per 1-mm Hg change	0.89	0.77–1.02	0.10

* HR = hazard ratio; 95% CI = 95% confidence interval; ERA = endothelin receptor antagonist; DLco = diffusing capacity for carbon monoxide; PVR = pulmonary vascular resistance; PAWP = pulmonary artery wedge pressure.

with initial treatment with a PDE5 inhibitor; hazard ratio [HR] 5.0, $P < 0.0001$), lower diffusing capacity for carbon monoxide (DLco) (HR 0.73 per 10% of predicted change [$P = 0.04$]), lower PAWP (HR 0.88 per 1-mm Hg change [$P = 0.02$]), lower cardiac output (HR 0.77 per 1-liter/minute change [$P = 0.03$]), higher PVR (HR 1.11 per Wood unit change [$P = 0.001$]), and a shorter time on initial therapy (HR 0.96 per 50 day change [$P = 0.05$]) (Table 2). In a multivariate analysis, the factors independently associated with a shorter TTCW were initial medication (ERA versus PDE5 inhibitor or ERA/PDE5 inhibitor; HR 2.63 [$P = 0.009$]), lower baseline DLco per 10% of predicted change (HR 0.69 per 10% of predicted change [$P = 0.04$]), and higher PVR per Wood unit change (HR 1.10 [$P = 0.007$]) (Table 3). When age, sex, and SSc disease duration were forced into the model, the results of the multivariate analysis were not appreciably changed. Additionally, when using forward selection or a sensitivity analysis to limit the number of variables, there was no significant change in the results (data not shown).

DISCUSSION

In this retrospective cohort study utilizing data from the prospective PHAROS registry of SSc patients with PAH, we observed that initial therapy with an ERA alone was associated with a worse outcome compared with initial treatment with either a PDE5 inhibitor alone or a combination of an ERA and a PDE5 inhibitor. This unexpected finding was not explained by differences in the measured baseline variables between the groups. After adjustment for other prognostic variables, initial ERA use was associated with a >2.5-fold increased risk of clinical worsening.

The optimal initial therapy for patients with SSc-related PAH is undefined. Although SSc patients have been included in most of the pivotal studies resulting in Food and Drug Administration approval for the currently available oral medications, there are limited analyses of the SSc subgroup. Furthermore, when such studies were analyzed, they often did not show signifi-

cant results, perhaps because the group sizes were relatively small. In the BREATHE-1 (Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension 1) trial, a subgroup analysis of 66 patients with connective tissue disease (CTD)-related PAH (84% with SSc) randomized to receive bosentan or placebo for 12–16 weeks showed a nonsignificant 19-meter improvement in the 6-minute walk distance favoring bosentan (7). In a subgroup analysis of the long-term SERAPHIN study of macitentan versus placebo, 185 patients with CTD-related PAH had a non-statistically significant improvement in morbidity and mortality while receiving the ERA (8).

In both the SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension 1) study and the PHIRST-1 (Pulmonary Arterial Hypertension and Response to Tadalafil 1) study, the subgroups with CTD-related PAH showed improvements in the 6-minute walk distance after 12 weeks of treatment with the PDE5 inhibitor (9,10). It is important to note that all of these studies compared the active agent with placebo (with or without background therapy) rather than performing head-to-head comparisons of ERA versus PDE5 inhibitor. Furthermore, with the exception of the SUPER-1 study (in which less than half of the CTD population had SSc), none of the other studies specified the proportion of patients with SSc-related PAH compared with patients with other types of CTD-related PAH. Because the response to therapy within subtypes of CTD-related PAH varies and favors patients with non-SSc-related PAH, the true response to therapy in SSc-related PAH populations is not well described in clinical trials (23). It does appear, however, that early recognition and treatment of PAH in SSc patients is associated with improved outcomes (24).

The recently published AMBITION study showed superiority for initial combination therapy with ambrisentan and tadalafil compared with either medication alone for the PAH group as a whole (25). Thirty-seven percent of the patients included in this study had CTD-related PAH, although the number of patients with SSc was not reported, and the effect in the CTD-related PAH subgroup in this trial is not yet fully described. It is important to highlight that patients with SSc-related PAH tend to respond less favorably to medical therapies that are beneficial in the PAH group as a whole (7,8), and that other CTD-related PAH subgroups, such as those with lupus (23), tend to have better responses compared with patients with SSc.

Although they are speculative, our findings may have also conflicted with those observed in the AMBITION study due to pharmacologic differences. The majority of patients initially receiving an ERA (67%) in the PHAROS study were treated with bosentan, which

is a nonselective ERA. As noted above, bosentan (the predominant ERA prescribed in our analysis) did not show a significant benefit in the CTD-related PAH subgroup in the BREATHE-1 study (7). Long-term blockade of the endothelin A receptor theoretically may be detrimental by promoting vasoconstriction and smooth muscle cell proliferation (26,27). Selective blockade of the endothelin B receptor in healthy individuals has been shown to cause increased renal vascular resistance, impaired clearance of endothelin by the kidneys, and increased levels of circulating endothelin 1 (28). This pharmacologic difference may limit extrapolation of our results to patients treated with the endothelin A-selective ERA ambrisentan (as in the AMBITION study) or macitentan, which is a nonselective ERA but has much higher affinity for the endothelin A receptor (29).

It is possible that our unexpected study results may be related to differences in patient characteristics between the groups. For example, if the patients who started therapy with ERAs were sicker at baseline, had a worse overall prognosis, or had a delay to amplification of therapy, this may explain their shorter TTCW and survival. However, there were no differences in any of the measured baseline characteristics or factors known to be associated with a poor prognosis, and the length of time until an additional agent was started was similar between the 3 groups. Additionally, ERA use was independently associated with worse outcomes even after adjusting for other prognostic factors.

We also utilized a landmark analysis with a 6-month landmark to minimize the biases in a time-to-event outcome inherent in this observational study. This method allows for an unbiased estimate of conditional time-to-event probabilities but is limited by the impact of the actual time landmark chosen, namely, an early landmark may lead to misclassification of events at a later time, while a late landmark may lead to the omission of a large number of events and thus result in a significant loss of power (14). Our selection of a 6-month landmark was based on data from the SERAPHIN study of macitentan in PAH (8). In this study, ~10% of treatment-naive subjects receiving study drug and nearly 30% of those receiving placebo experienced clinical worsening by 6 months, highlighting the clinical relevance of this time point. Selection of this time point as the landmark minimizes the bias introduced by inclusion of patients in the study who have poorer prognoses and are more likely to have clinical worsening early regardless of the intervention.

Our analysis could not provide answers to any mechanistic questions, but pharmacologic factors could explain the worse outcomes seen in the patients initially

treated with ERAs. Fluid retention is a common side effect of ERAs, occurring in 6–28% of patients in clinical studies (30,31), and has even been severe enough to cause drug discontinuation (32). This potential for fluid retention may have driven TTCW events such as PAH-related hospitalization and prostacyclin initiation. Another potential mechanistic difference is the influence of PDE5 inhibition on right ventricular structure (33,34), because changes in the right ventricle are a strong determinant of outcomes in patients with PAH (35–37).

The current study has several strengths. As opposed to most prior drug treatment studies that assessed effects only over a short period of time (12–20 weeks), this study had long-term followup (mean of 2.4 years for the survival analysis). Medications that have benefit over a short time period may have detrimental effects that do not become evident until there is longer-term exposure. Additionally, our patients were carefully characterized at baseline, and followup for survival was 88%.

The current study also has limitations. Although the registry data were collected prospectively, the analysis was retrospective and therefore has inherent limitations. Although we adjusted for many prognostic variables, there may be unmeasured factors that were unbalanced between groups and led to the differential outcomes. In particular, right atrial pressure values, which represent a well-described prognostic factor (20,21,38), were not obtained in this data set, although other important baseline hemodynamic variables were not statistically different between the 3 groups. Although the number of patients in our study was larger than that in most prior subgroup analyses of patients with SSc-related PAH, the sample size was still small, and there is a risk of Type II error, in that we may not have identified differences in confounding baseline characteristics (e.g., DLco) that may have driven the results. Our results are not definitive and require further study.

By excluding patients with fewer than 6 months of followup, we may have introduced bias against sicker patients who may have died sooner. As discussed above, we chose this landmark analysis approach (14) to estimate time-to-event probabilities in an unbiased manner. Of the 17 patients who were excluded because they had fewer than 6 months of followup, 9 had only 1 study visit. Of the 8 patients who died prior to 6 months, 6 were receiving prostanoid therapy and thus would have been excluded from this analysis even if they had 6 months of followup.

A limited number of deaths occurred during the observation period; therefore, we were unable to perform a separate Cox regression analysis for survival. However, the rate of death appeared to be higher in the group that received initial therapy with an ERA. The limited number of events may be explained by the fact

that the PHAROS study was conducted at SSc centers that focused on early detection and treatment of PAH. The effect of the preference of a clinical center or an individual practitioner for initial oral therapy may have influenced the results; however, the large number of centers prevents controlling for these factors. Because some patients progressed to treatment with a second oral agent, some progressed to treatment with an inhaled prostanoid, and some received parenteral therapy, a time-varying analysis was not performed. Last, outcomes such as hospitalization and initiation of parenteral prostacyclins were not protocolized; nonetheless, we believe that this approach could be a strength, because it may more accurately represent clinical care.

Compared with treatment with a PDE5 inhibitor or combined treatment with an ERA and a PDE5 inhibitor, initial therapy with ERA was associated with a significantly shorter 3-year TTCW and survival in patients with SSc-related PAH, even after controlling for other prognostic variables. This study highlights the need for randomized controlled trials performing head-to-head comparisons between PAH-specific medications specifically in patients with SSc as well as registry studies with long-term clinical followup to properly define “real world” outcomes.

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. Lammi 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. Lammi, Mathai, Saketkoo, Domsic, Furst, Steen.

Acquisition of data. Lammi, Mathai, Bojanowski.

Analysis and interpretation of data. Lammi, Mathai, Furst, Steen.

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