Comparison of Treatment Response in Idiopathic and Connective Tissue Disease–associated Pulmonary Arterial Hypertension

Rennie L. Rhee¹, Nicole B. Gabler², Sapna Sangani¹, Amy Praestgaard², Peter A. Merkel^{1,2}, and Steven M. Kawut^{2,3}

¹Division of Rheumatology, ²Center for Clinical Epidemiology and Biostatistics, and ³Pulmonary, Allergy, and Critical Care Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Rationale: Studies suggest that patients with connective tissue disease–associated pulmonary arterial hypertension (CTD-PAH) have a poorer treatment response to therapies for PAH compared with patients with idiopathic PAH (IPAH), but individual randomized controlled trials (RCTs) have been underpowered to examine differences within these subgroups.

Objectives: To compare the effect of therapy for PAH in CTD-PAH versus IPAH.

Methods: We obtained individual participant data from phase III placebo-controlled RCTs of therapies for PAH submitted to the U.S. Food and Drug Administration for drug approval. A treatment-by-diagnosis interaction term evaluated differences in treatment response between CTD-PAH and IPAH. Outcomes included change in 6-minute-walk distance (Δ 6MWD) from baseline to 12 weeks, clinical worsening, and all-cause mortality.

Measurements and Main Results: The study sample included 827 participants with CTD-PAH and 1,935 with IPAH from 11 RCTs. Patients with CTD-PAH had less improvement in 6MWD when assigned to active treatment versus placebo compared with patients with IPAH (difference in treatment effect on Δ 6MWD in CTD-PAH vs. IPAH, -17.3 m; 90% confidence interval, -31.3 to -3.3 ; P for interaction = 0.043). Treatment was less effective in reducing the occurrence of clinical worsening in CTD-PAH versus IPAH (P for interaction = 0.012), but there was no difference in the placebo-adjusted effect of treatment on mortality (P for interaction = 0.65).

Conclusions: Treatment for PAH was less effective in CTD-PAH compared with IPAH in terms of increasing 6MWD and preventing clinical worsening. The heterogeneity of treatment response supports the need for identifying therapies that are more effective for CTD-PAH.

Keywords: pulmonary hypertension; clinical trial; meta-analysis

Pulmonary arterial hypertension (PAH) is a severe and often fatal complication of connective tissue diseases (CTDs). PAH is known to occur in systemic sclerosis (SSc); systemic lupus erythematosus; mixed CTD; and to a lesser extent rheumatoid arthritis, inflammatory myositis, and Sjögren's syndrome (1, 2). Compared with those with idiopathic PAH (IPAH), patients with CTD-PAH have poorer outcomes and worse survival (3–6). Among CTDs, SSc is

the most common setting for PAH, which is the leading cause of death (1, 7).

Prior studies have examined whether targeted therapy for PAH improves morbidity in patients with CTD-PAH to the same extent as that seen in IPAH (8–20). These studies were limited by inadequate comparators, small sample sizes, the use of unvalidated outcomes, and (in the case of epidemiologic studies) the possibility of lead-time and length-time bias caused by

screening for PAH in patients with SSc (21). Patients with CTD-PAH are more likely to have pulmonary venous changes in addition to the characteristic pulmonary arterial changes seen in IPAH (22, 23) and have extrapulmonary complications, such as arthritis, limited mobility, and deconditioning (16, 20). Additional comorbidities, such as interstitial lung disease and recurrent aspiration resulting from esophageal dysmotility, may also

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Correspondence and requests for reprints should be addressed to Rennie L. Rhee, M.D., Division of Rheumatology, 5 White, Rheumatology Suite, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: rennie.rhee@uphs.upenn.edu

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At a Glance Commentary

Scientific Knowledge on the

Subject: Although it is well-known that patients with connective tissue disease–associated pulmonary arterial hypertension (CTD-PAH) have a poorer prognosis compared with idiopathic IPAH, no study has determined whether response to treatment differs between these two groups.

What This Study Adds to the

Field: Treatment is less effective in patients with CTD-PAH enrolled in clinical trials of therapy for PAH compared with patients with idiopathic PAH. Identification of better treatments is needed for patients with CTD-PAH.

affect clinical outcomes and treatment response (24, 25). For these reasons, whether targeted treatment for PAH has the same effect in CTD-PAH and IPAH is unknown.

Understanding heterogeneity in treatment effects has become a major research priority (26), and completed randomized clinical trials (RCTs) are a rich source for comparative effectiveness studies. There is a growing interest in sharing individual participant data from clinical trials (27), which when combined can achieve the power needed to examine differential treatment effects across subgroups of patients. We leveraged participant data from 11 RCTs to evaluate whether treatment response heterogeneity exists between patients with CTD-PAH compared with IPAH. We hypothesized that treatment for PAH is less effective compared with placebo in CTD-PAH versus IPAH in terms of improving 6-minute-walk distance (6MWD) and reducing clinical worsening. Some of the results of this study have been previously reported in the form of an abstract (28).

Methods

Data Sources and Study Selection

We obtained individual participant data from phase III randomized placebo-controlled trials of therapies for PAH that were submitted from 2000 through 2013 to the U.S. Food and Drug Administration

(FDA) for drug approval. We included trials of treatments that were subsequently not approved by the FDA (e.g., sitaxsentan) because our interest focused on comparative effectiveness rather than specific drugs. To adjust for baseline differences in cardiopulmonary hemodynamics, we excluded five trials that did not routinely collect data from right heart catheterization at baseline (29–33). The study sample therefore consisted of 11 trials studying eight drugs: (1) ambrisentan (ARIES-1 and ARIES-2), (2) bosentan (BREATHE-1), (3) iloprost (AIR), (4) macitentan (SERAPHIN), (5) riociguat (PATENT-1), (6) sildenafil (SUPER), (7) sitaxsentan (STRIDE-1, STRIDE-2, and STRIDE-4), and (8) subcutaneous treprostinil (34–43).

These multicenter, international trials enrolled patients diagnosed with PAH, requiring a mean pulmonary arterial pressure greater than or equal to 25 mm Hg and a pulmonary capillary wedge pressure less than or equal to 15 mm Hg. For this analysis, only patients with CTD-PAH or IPAH (including heritable PAH) were included. All trials randomized patients to either active drug or placebo; all dosing arms of the active drug were combined into a single active treatment arm. STRIDE-2 had an open-label bosentan treatment arm that was excluded from this study. Duration of study treatment among the trials was between 12 and 18 weeks except for SERAPHIN, which had a mean treatment period of 96 weeks. BREATHE-1 consisted of two trial periods: all patients participated in period one (16 wk) and only patients enrolled in the first 2 months (48 patients) participated in period two, which continued the double-blind treatment for an additional 12 weeks (total study duration, 28 wk); data from both periods were included in this study.

Data Extraction and Quality Assessment

Anonymized patient data were provided by the FDA. Data were reviewed for consistency with published reports and for missing items. Information about the trials was cross-checked with published reports, trial protocols, and data collection sheets. To assess randomization integrity, we assessed patterns of treatment allocation and balance of baseline characteristics by treatment and diagnostic group. Any inconsistencies were resolved with the relevant trial contact. We

assessed risk of bias by using the Cochrane Collaboration's "risk-of-bias" tool (44).

Outcomes

Outcomes included (1) Δ 6MWD from baseline to Week 12, (2) first occurrence of clinical worsening, and (3) all-cause mortality. For this study we limited the definition of clinical worsening to several clinically meaningful events specific to PAH: hospitalization for PAH, initiation of rescue therapy for PAH, lung transplant, atrial septostomy, right heart failure, or death. We excluded worsening 6MWD and functional class. The imputation methods used to address missing 12-week 6MWD data are available in Table E1 in the online supplement.

Statistical Analyses

For comparison of the baseline characteristics, we used Student's *t* test and chi-square test for continuous and categorical data, respectively. We used linear or logistic regression to examine the effect of treatment on outcomes. Trials were pooled using random-effects modeling to account for potential variability between trials. We used a treatment-by-diagnosis interaction term in the model to determine if diagnosis (CTD-PAH vs. IPAH) modified the effect of assigned treatment (active drug vs. placebo, using the intention-to-treat principle) on outcome. We *a priori* adjusted for age, sex, race, study, body mass index, and baseline 6MWD, World Health Organization (WHO) functional class, right atrial pressure, cardiac index, mean pulmonary artery pressure, serum creatinine, and hemoglobin, and the main effects of treatment and diagnosis in the regression analyses examining Δ 6MWD and clinical worsening. These potential confounders were selected based on their association with PAH outcomes in previous publications (9, 11, 45).

Models examining Δ 6MWD were adjusted for baseline 6MWD, which allowed for the comparison of absolute differences in 6MWD. We adjusted the analysis of mortality for fewer covariates *a priori* (age, sex, treatment, diagnosis, and baseline 6MWD and pulmonary vascular resistance) to avoid overfitting the model. Multiple imputation was used for those with missing baseline 6MWD, right atrial pressure, mean pulmonary arterial pressure, cardiac index, serum creatinine, and hemoglobin (*n* = 145). The imputation

model included age, sex, race, diagnosis, treatment, and baseline WHO functional class, and 20 imputed data sets were generated.

We assessed between-study heterogeneity for pooled outcomes using a two-stage inverse-variance random-effects model and the I^2 test for heterogeneity was determined. A secondary analysis compared the subgroup of patients with SSc-PAH with IPAH. Sensitivity analyses included additional adjustment for medications (background therapy for PAH, anticoagulation, oral glucocorticoids, and other immunosuppressive agents) and comorbidities and exclusion of clinical worsening events and deaths after 18 weeks in the SERAPHIN trial.

A significance level of 0.10 was used *a priori* for interaction terms and a significance level of 0.05 was used for all other tests of hypotheses (46–48). All analyses used Stata version 12.1 (StataCorp, College Station, TX).

Role of the Trial Sponsors and Funding Source

The sponsors of the trials reviewed the final manuscript but had no role in the analysis and interpretation of data, preparation of the manuscript, or decision to submit the manuscript for publication. The funding source had no other role in the study. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. This study was considered exempt by the Institutional Review Board of the University of Pennsylvania.

Results

Patient and Trial Characteristics

A total of 2,762 patients were included in the study sample; 827 were diagnosed with CTD-PAH and 1,935 with IPAH. Among the patients with CTD-PAH, 465 (56%) had SSc (limited or diffuse cutaneous SSc), 121 (15%) had systemic lupus erythematosus, 86 (10%) had mixed CTD, 79 (10%) had Sjögren's syndrome, 17 (2%) had an overlap syndrome, and the remaining 59 (7%) had another CTD. Compared with IPAH, patients with CTD-PAH had less affected baseline hemodynamics and lower baseline 6MWD (Table 1). Patients with SSc-PAH were similar to the overall CTD-PAH group. Baseline characteristics of the

patients in the treatment and placebo groups within the diagnostic categories of CTD-PAH and IPAH were similar (*see* Table E2).

Details of the trials are shown in Table E3. Most of the trials were studies of endothelin receptor antagonists (including 1,614 [59%] participants) (*see* Table E4). No issues with the integrity of the individual participant data were identified. Risk of bias was determined to be low with adequate randomization and allocation concealment procedures, masking of participants and researchers, and reporting of all prespecified outcomes.

Change in 6MWD at 12 Weeks

There was a significant difference in treatment-related improvement in the 6MWD between CTD-PAH and IPAH. The mean placebo-corrected treatment effect in Δ 6MWD was 23.1 m in patients with CTD-PAH compared with 40.4 m in patients with IPAH (Table 2) (adjusted difference in the treatment effect, -17.3 m; 90% confidence interval [CI], -31.3 to -3.3 ; P for interaction = 0.043). Patients with IPAH assigned to active treatment compared with CTD-PAH had greater improvements at all thresholds of Δ 6MWD (Figure 1).

The difference in the treatment effect between SSc-PAH and IPAH was -4.2 m (90% CI, -21.8 to 13.3 ; P for interaction = 0.69) after adjusting for potential confounders (*see* Table E5). When medications or comorbidities were included in the regression analyses, results were similar for both CTD-PAH and SSc-PAH in comparison with IPAH (*see* Table E6). A two-stage model showed similar results and there was no evidence of heterogeneity between trials for Δ 6MWD ($I^2 = 8.7\%$; $P = 0.36$) (*see* Figure E1).

Clinical Worsening

There were 117 (14%) patients with CTD-PAH and 260 (13%) patients with IPAH who developed clinical worsening during the trial period. The most common clinical worsening events were initiation of rescue therapy for PAH, hospitalization for PAH, and death (*see* Table E7). Assignment to active treatment reduced the risk of clinical worsening compared with placebo even after adjusting for potential confounders (odds ratio [OR], 0.44; 95% CI, 0.35–0.56; $P < 0.001$). However, the effect of active treatment compared with placebo on

clinical worsening was significantly different in CTD-PAH versus IPAH. Among patients with IPAH, active treatment reduced the risk of clinical worsening compared with placebo (OR, 0.34; 95% CI, 0.25–0.48), whereas no difference was seen among patients with CTD-PAH (OR, 0.72; 95% CI, 0.45–1.16; P for interaction = 0.012) (Figure 2; *see* Table E8).

Sixty (13%) patients with SSc-PAH developed clinical worsening. The effect of treatment on clinical worsening compared with placebo was significantly different in SSc-PAH versus IPAH after adjusting for potential confounders (P for interaction = 0.097) (Figure 2; *see* Table E7).

Results were similar after we adjusted for medications or comorbidities (*see* Table E9). Limiting follow-up to 18 weeks in the SERAPHIN trial led to similar results when comparing CTD-PAH with IPAH, whereas no difference was found between SSc-PAH and IPAH. There was no evidence of heterogeneity between trials for clinical worsening ($I^2 = 0.0\%$; $P = 0.59$) (*see* Figure E2).

Death

Twenty-eight (3%) patients with CTD-PAH and 55 (3%) patients with IPAH died during the study period. Patients with CTD-PAH had a higher risk of death than that of patients with IPAH (OR, 1.95; 95% CI, 1.27–3.02; $P = 0.011$), and there was no significant treatment effect on mortality in the overall cohort (OR, 0.78; 95% CI 0.53–1.16; $P = 0.30$). Furthermore, diagnosis (CTD-PAH vs. IPAH) did not modify the effect of treatment on mortality (P for interaction = 0.65) (*see* Table E8 and Figure E3). Sixteen (4%) patients with SSc-PAH died, and there was no difference in the treatment effect on mortality between SSc-PAH and IPAH (P for interaction = 0.58) (*see* Table E8 and Figure E3).

Discussion

This is the first study to compare treatment effects in CTD-PAH and IPAH using individual participant data from multiple RCTs across all drug classes currently used in PAH. Results from this study show that advanced therapy for PAH is less effective in CTD-PAH compared with IPAH in improving short-term 6MWD and

Table 1. Patient Characteristics by Diagnosis

Characteristic	CTD-PAH						P Value CTD-PAH vs. IPAH
	All (n = 827)		SSc-PAH (n = 465)		IPAH (n = 1,935)		
	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	
Age, yr	827	53 (14)	465	59 (11)	1,935	47 (16)	<0.001
Female sex, %	827	89	465	88	1,935	73	<0.001
Race: white/black/other, %	827	70/4/26	465	88/3/9	1,935	71/4/25	0.76
BMI, kg/m ²	827	26 (6)	465	27 (6)	1,932	27 (7)	<0.001
WHO class III-IV, %	826	54	464	63	1,935	56	0.36
Comorbidities, %	827		465		1,935		
Coronary artery disease		8		10		8	0.58
Diabetes mellitus		5		4		9	<0.001
Hypertension		39		45		30	<0.001
Hyperlipidemia		15		19		14	0.69
Thyroid disease		21		24		14	<0.001
Thromboembolic disease		5		4		4	0.13
Gastrointestinal reflux		23		31		7	<0.001
Received background treatment for PAH, %	827	24	465	22	1,935	21	0.040
Prostacyclin analog		2		3		2	0.75
ERA		8		9		6	0.13
PDE5i		15		11		14	0.45
Anticoagulant therapy, %	827	65	465	64	1,935	81	<0.001
Oral glucocorticoid therapy, %	827	48	465	35	1,935	7	<0.001
Immunosuppressive therapy,* %	827	22	465	12	1,935	1	<0.001
Hemoglobin, g/L	803	138 (19)	451	136 (19)	1,885	151 (21)	<0.001
Serum creatinine, μmol/L	811	80 (26)	454	86 (28)	1,914	82 (24)	0.18
Hemodynamics							
RAP, mm Hg	811	7.9 (4.9)	460	8.1 (4.9)	1,905	9.3 (5.8)	<0.001
mPAP, mm Hg	824	46 (12)	463	44 (13)	1,934	55 (16)	<0.001
CI, L/min/m ²	819	2.5 (0.8)	462	2.5 (0.8)	1,905	2.3 (0.7)	<0.001
PCWP, mm Hg	809	9 (3)	458	9 (3)	1,880	9 (4)	0.81
PVR, Wood units	813	9.9 (6.0)	459	9.2 (6.1)	1,873	13.0 (7.6)	<0.001
6-minute-walk distance, m	826	351 (124)	464	336 (123)	1,935	365 (135)	0.011

Definition of abbreviations: BMI = body mass index; CI = cardiac index; CTD-PAH = connective tissue disease–associated pulmonary arterial hypertension; ERA = endothelin receptor antagonist; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary arterial pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PDE5i = phosphodiesterase type 5 inhibitor; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SSc-PAH = systemic sclerosis–associated pulmonary arterial hypertension; WHO = World Health Organization.

*Not including glucocorticoids.

reducing the risk of clinical worsening. Similar results were found when comparing the subgroup of patients with SSc-PAH with IPAH.

Several individual clinical trials examined the treatment effect in CTD-PAH but these were limited by small samples

(14, 15, 17, 19, 49). Two prior meta-analyses found disparate results when examining the treatment effect of therapies for PAH in CTD-PAH (13, 18). This individual participant data meta-analysis has many advantages over these traditional aggregate data meta-analyses, including

standardization of analysis, better adjustment for confounders and baseline risk, and imputation of missing data. Our study leveraged the ability to study interactions and assess differential treatment effects in patient subgroups that would not be possible

Table 2. Comparison of Placebo-corrected Treatment Effect on Change in 6-Minute-Walk Distance between CTD-PAH and IPAH

	CTD-PAH (n = 827)	IPAH (n = 1,935)	Difference-in-Difference (90% CI)	P Value for Interaction
Change in 6-minute-walk on active treatment, m	9.6	30.1		
Change in 6-minute-walk on placebo, m	−13.5	−10.3		
Treatment – Placebo, m	23.1	40.4	−17.3 (−31.3 to −3.3)	0.043

Definition of abbreviations: CI = confidence interval; CTD-PAH = connective tissue disease–associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension.

Adjusted for age, sex, race, body mass index, study, baseline 6-minute-walk distance, World Health Organization functional class, baseline right atrial pressure, mean pulmonary artery pressure, cardiac index, serum creatinine, and hemoglobin.

Figure 1. Cumulative change in 6-minute-walk distance ($\Delta 6\text{MWD}$) stratified by treatment and diagnosis. Reverse cumulative distribution curves of $\Delta 6\text{MWD}$ among patients with (1) IPAH assigned to active treatment (blue line), (2) CTD-PAH assigned to active treatment (red line), (3) IPAH assigned to placebo (green line), and (4) CTD-PAH assigned to placebo (yellow line). Extreme values ($\Delta 6\text{MWD} < -250$ and $\Delta 6\text{MWD} > 250$) are not depicted. P for treatment-by-diagnosis interaction = 0.043. Adjusted for age, sex, race, body mass index, study, baseline 6MWD, World Health Organization functional class, baseline right atrial pressure, mean pulmonary artery pressure, cardiac index, serum creatinine, and hemoglobin. CTD-PAH = connective tissue disease–associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension.

in an aggregate data meta-analysis. An individual participant data meta-analysis avoids the potential for ecologic bias. Lastly, pooling data from multiple clinical trials also enabled us to evaluate both intermediate and definitive clinical endpoints.

There was a complex relationship between diagnosis, hemodynamics, and 6MWD as shown in previous studies (3, 9). Patients with CTD-PAH had less affected hemodynamics but a significantly worse baseline 6MWD compared with patients with IPAH. Although differences in

Figure 2. Adjusted odds ratios (95% confidence interval) of clinical worsening in treatment versus placebo groups stratified by diagnosis. Adjusted for age, sex, race, body mass index, study, baseline 6-minute-walk distance, World Health Organization functional class, baseline right atrial pressure, mean pulmonary artery pressure, cardiac index, serum creatinine, and hemoglobin. P values represent P for interaction of treatment group and diagnosis. CTD-PAH = connective tissue disease–associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; SSc-PAH = systemic sclerosis–associated pulmonary arterial hypertension.

treatment effect were seen between CTD-PAH and IPAH for the outcome of $\Delta 6\text{MWD}$, many controversies exist regarding the use of 6MWD to assess treatment response. The 6MWD has not been validated as a surrogate outcome in PAH and exercise capacity in CTD-PAH is affected by extrapulmonary comorbidities related to the underlying CTD including arthritis, limited mobility, and deconditioning (8, 16, 50, 51). Furthermore, the minimal clinically important difference for 6MWD in CTD-PAH or SSc-PAH is not known. Clinical worsening, however, is a clearly relevant endpoint and is potentially less influenced by noncardiopulmonary manifestations of CTD. We excluded 6MWD or WHO functional class changes in the definition of clinical worsening to focus on definitive clinical outcomes and minimize confounding caused by noncardiopulmonary comorbidities in CTD. The finding that allocation to active treatment was more effective in reducing clinical worsening in IPAH compared with CTD-PAH or SSc-PAH provides firm evidence that treatment effect heterogeneity exists in PAH.

It is well established that patients with CTD-PAH and SSc-PAH have a worse outcome compared with patients with IPAH (3–6). Our results suggest that such differences could be explained in part by a poorer response to treatment. Patients with CTDs are more likely to develop interstitial lung disease, pulmonary venous disease, or heart disease, which in turn may reduce efficacy of PAH therapies (22, 23). More rigorous screening measures may be needed to exclude patients with these concurrent issues from clinical trials. In addition, CTD-PAH is comprised of a heterogeneous group of disorders and different disease subtypes within CTD-PAH may benefit from treatment more than others.

There are several potential implications for the design of future trials of PAH therapy. Considering the lower effectiveness of therapies in patients with CTD-PAH, excluding patients with CTD-PAH may magnify the anticipated effect size, thereby reducing the sample size, costs, and time to enroll, while maintaining adequate power. However, this may not be the optimal approach. Active treatment did increase the 6MWD in patients with CTD-PAH, albeit to a lesser extent compared with IPAH. The FDA, European Medicines Agency, and other regulatory bodies accept the 6MWD

for approval of drugs in PAH so that a significant effect of active treatment on the 6MWD may be sufficient for approval in this population, even if the clinical implication of the effect is unclear. CTD-PAH accounted for 25% of all patients in our study and is one of the most common forms of PAH in epidemiologic studies (52), so that the incorporation of these patients in clinical trials would allow them to be included in the labeling and indications for novel treatments for PAH. Although it is premature to use these results in guiding clinical care, clinicians should recognize the differential benefits of therapies and consider the prognosis for patients with various forms of PAH.

Our study has several potential limitations. Standard classification criteria were not used to identify CTDs, which may have led to misclassification bias. However, differences in the baseline characteristics between the patients with CTD-PAH and IPAH were similar to what has been seen in prior studies (3, 4), and if present,

misclassification would likely be nondifferential in terms of the outcome and would bias toward the null hypothesis, resulting in an underestimation of true differences. We did not perform a systematic review of all published and unpublished trials and excluded five trials without baseline hemodynamic data, two of which were “negative” trials. The predominance of “positive” trials submitted to the FDA and in this study may therefore have potentially led to selection bias. The durations of the trials generally ranged between 12 and 18 weeks, which limited examination of long-term effects. In a small percentage of patients with loss to follow-up (4%), missing 12-week 6MWD values were replaced using the last observation carried forward. Although having the potential for bias (53), missing data replaced by this method were unlikely to have significantly affected the results given the very small rate of loss to follow-up (54). In the individual trials, clinical worsening was not always centrally adjudicated and its

definition varied across studies; however, because treatment was randomized and blinded, variability in the definition of clinical worsening was unlikely to have biased results away from the null.

In conclusion, current classes of advanced therapies for PAH are less effective in CTD-PAH compared with IPAH in patients enrolled in clinical trials. The implementation of classification criteria for the individual CTDs and use of rigorous screening measures to exclude other causes of pulmonary hypertension may be needed to elucidate differences in treatment response in CTD-PAH. Further studies are needed to better understand the pathophysiology of CTD-PAH and identify therapies that are more effective for CTD-PAH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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