Adverse Events in Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

Rennie L. Rhee, MD, MSCE, **Nicole B. Gabler, PhD, MHA**, **Amy Praestgaard, MS**, **Peter A. Merkel, MD, MPH**, and **Steven M. Kawut, MD, MS**
University of Pennsylvania Perelman School of Medicine, Philadelphia

Abstract

Objective—Patients with connective tissue disease (CTD)–associated pulmonary arterial hypertension (PAH) have a poorer prognosis compared to those with idiopathic PAH, but little is known about the differences in treatment-related adverse events (AEs) and serious adverse events (SAEs) between these groups. This study was undertaken to characterize these differences.

Methods—Individual patient-level data from 10 randomized controlled trials of therapies for PAH were obtained from the US Food and Drug Administration. Patients diagnosed as having either CTD-associated PAH or idiopathic PAH were included. A treatment-by-diagnosis interaction term was used to examine whether the effect of treatment on occurrence of AEs differed between patients with CTD-associated PAH and those with idiopathic PAH. Studies were pooled using fixed-effect models.

Results—The study sample included 2,370 participants: 716 with CTD-associated PAH and 1,654 with idiopathic PAH. In the active treatment group compared to the placebo group, the risk of AEs was higher among patients with CTD-associated PAH than among those with idiopathic PAH (odds ratio [OR] 1.57, 95% confidence interval [95% CI] 1.00–2.47 versus OR 0.94, 95% CI 0.69–1.26; P for interaction = 0.061), but there was no difference in the risk of SAEs in analyses adjusted for age, race, sex, hemodynamic findings, and laboratory values. Despite the higher occurrence of AEs in patients with CTD-associated PAH assigned to active therapy compared to those receiving placebo, the risk of drug discontinuation due to an AE was similar to that in patients with idiopathic PAH assigned to active therapy (P for interaction = 0.27).

Conclusion—Patients with CTD-associated PAH experienced more treatment-related AEs compared to those with idiopathic PAH in therapeutic clinical trials. These findings suggest that the overall benefit of advanced therapies for PAH may be attenuated by the greater frequency of AEs.

Address correspondence to Rennie L. Rhee, MD, MSCE, Division of Rheumatology, 8th Floor Penn Tower, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. rennie.rhee@uphs.upenn.edu.

Pulmonary arterial hypertension (PAH) is a severe and often fatal complication of connective tissue diseases (CTDs). Among the CTDs, systemic sclerosis (SSc) is the most common setting for PAH, with a reported prevalence of 7–12% based on the proportion of patients undergoing right-sided heart catheterization (1–3), and PAH is the leading cause of death in patients with SSc (4,5). PAH is also known to occur in systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), overlap syndromes, and, to a lesser extent, rheumatoid arthritis and Sjögren's syndrome (2,6–9). Compared to patients with idiopathic PAH, patients with CTD-associated PAH have a higher mortality and a lower walking distance on the 6-minute walk test, higher levels of B-type natriuretic peptide, worse right ventricular function, more left-sided heart dysfunction, lower lung function, and more pericardial disease (10–20).

Clinical trials of therapies for PAH have often included both CTD-associated PAH and idiopathic PAH. Although prior studies have evaluated differences in efficacy (21,22), little attention has been paid to differences in adverse events (AEs) between CTD-associated PAH and idiopathic PAH. The reporting of AEs is an important and required component of clinical trials from both the perspective of protection of human subjects and the safety profile of an experimental drug. The US Food and Drug Administration (FDA) Code of Federal Regulations defines an AE as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related" (23). In addition, a serious AE (SAE) is an AE that, according to the investigator or sponsor, results in death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent and significant inability to conduct normal life functions, or a congenital anomaly or birth defect. The nature and frequency of AEs are important factors when deciding on the regulatory approval of a new medication or when physicians and patients are making decisions regarding initiation or maintenance of treatments.

The potential for both treatment-related and non–treatment-related AEs and SAEs may be greater in patients with multiorgan systemic diseases (24,25). Understanding the AE profile in patients with CTD-associated PAH compared to patients with idiopathic PAH in clinical trials could inform the design of future clinical trials, influence the monitoring of drug toxicities in patients who are receiving therapy, provide insight into improving compliance, and better help physicians and patients consider the comparative effectiveness and risk of treatment. The purpose of this study was to compare the risk of AEs and SAEs between patients with CTD-associated PAH and those with idiopathic PAH enrolled in clinical trials.

PATIENTS AND METHODS

Study population

De-identified individual patient data were obtained from the databases of phase III placebo-controlled, randomized trials submitted to the FDA through 2013 that tested endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE5) inhibitors, and prostacyclin analogs for the treatment of PAH. Only patients with a diagnosis of idiopathic PAH or CTD-associated PAH, as determined by the investigators in each study, were included in the analysis.

Ten clinical trials that studied 7 agents (ambrisentan, bosentan, iloprost, macitentan, sildenafil, sitaxsentan, and treprostinil) were included (26–34). The BREATHE-2 (Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension 2) and AIR-2 (Aerosolized Iloprost Randomized Study 2) trials were excluded, since they were not phase III trials. In addition, 5 trials that did not routinely collect baseline hemodynamic data were also excluded (35–41). All trials had at least a 12-week treatment period. Trials of treatments that were subsequently not approved by the FDA (e.g., sitaxsentan) were included, since this was a study of clinical trial populations rather than specific drugs. All included trials reported similar inclusion criteria, outcomes, followup time, and methods, except the trial investigating macitentan, which was an event-driven study design (34). Because the followup time was notably longer in the macitentan trial (mean duration of followup >1 year), we examined only the AEs that occurred in the first 18 weeks of followup, to be consistent with the other studies.

Exposure

The primary exposure was the differential treatment effect between CTD-associated PAH and idiopathic PAH. Therefore, a treatment-by-diagnosis interaction was included to assess whether diagnosis (CTD-associated PAH versus idiopathic PAH) modified the effect of treatment (active therapy versus placebo) on the outcome. A subgroup analysis was performed among patients with CTD who were diagnosed as having SSc (limited or diffuse), and these patients were compared to patients with idiopathic PAH. All trials contained CTD subtype except for the macitentan trial; for that study, CTD subtype was derived from the medical history.

Outcomes

The primary outcome of interest was the occurrence of AEs (yes versus no) during the trial period. Secondary outcomes included the rate of AEs, occurrence of an SAE (yes versus no), and the rate of SAEs. AEs and SAEs were then categorized into specific groups, such as infection, headache, and rash. The 10 most common AE and SAE types were identified and the occurrence of each of these AE and SAE types was examined. Discontinuation of the study drug due to an AE or SAE was also examined.

Statistical analysis

Patient characteristics were summarized for the entire group as well as by diagnosis (CTD-associated PAH or idiopathic PAH) and CTD subgroup (SSc-associated PAH). Results are expressed as the mean ± SD for normally distributed continuous variables, median and inter-quartile range for non-normally distributed variables, and percentages for categorical variables. Comparisons between patients with CTD-associated PAH and those with idiopathic PAH were made using Student's *t*-test for continuous variables and chi-square test for categorical variables.

Evaluation for between-study heterogeneity was performed using a 2-stage inverse-variance individual participant data meta-analysis, and the I_2 test for heterogeneity was determined. Due to the lack of significant heterogeneity between studies, data from the studies were pooled using a fixed-effect model. To examine the outcomes, logistic regression was used

for binary outcomes, such as occurrence of AEs/SAEs and occurrence of discontinuation of the study drug due to AEs/SAEs. Negative binomial regression was used for count data (rates of AEs and SAEs) to analyze the number of AEs or SAEs during the followup period, accounting for over-dispersion. Adjustments were made a priori for age, race, sex, study, body mass index (BMI), baseline 6-minute walk distance, baseline World Health Organization (WHO) functional class, baseline hemodynamics (cardiac index, mean pulmonary arterial pressure, right atrial pressure), and baseline laboratory values (creatinine and hemoglobin levels). These potential confounders were selected on the basis of prior observations of their association with PAH outcomes (12,14,42–44). Regression models were not used to analyze the individual SAE types, given the low number of events.

The relationships between treatment allocation and outcome with effect modification by diagnosis (CTD-associated PAH and idiopathic PAH) or diagnosis subgroup (SSc-associated PAH and idiopathic PAH) were examined. If the treatment-by-diagnosis interaction term was not significant, then the association of diagnosis (CTD-associated PAH versus idiopathic PAH) with the outcome (number or rate of AEs and SAEs) was evaluated independently, with adjustment for potential confounders, including a coded value for active treatment versus placebo. Interactions were also examined after stratifying by drug type (ERA, PDE5 inhibitor, and prostacyclin analog). A significance level of 0.10 was used for interaction terms, and a significance level of 0.05 was used in all other hypothesis tests (45).

All analyses were conducted using Stata (version 12.1; StataCorp). The study was exempt from review by the institutional review board of the University of Pennsylvania because we used existing de-identified patient data, which are not considered part of the definition of human subjects research.

RESULTS

Patient characteristics

There were 2,822 patients in the 10 trials, of whom 2,370 met the inclusion criteria. There were 716 patients with CTD-associated PAH and 1,654 with idiopathic PAH (Table 1). Among the patients with CTD-associated PAH, 407 (57%) had SSc, 100 (14%) had SLE, 80 (11%) had MCTD, 69 (10%) had Sjögren's syndrome, 21 (3%) had an overlap syndrome, and 39 (5%) were classified as having another CTD. Patients with CTD-associated PAH were significantly older, more often female, and had a significantly lower baseline 6-minute walk distance compared to patients with idiopathic PAH. The proportions of patients in each WHO functional class at baseline were similar between the 2 diagnoses, and patients with CTD-associated PAH had significantly better baseline hemodynamics, including lower right atrial pressure, lower mean pulmonary arterial pressure, higher cardiac index, and lower pulmonary vascular resistance (Table 1). There were 1,614 patients (68%) enrolled in trials of ERAs, 259 (11%) in trials of PDE5 inhibitors, and 497 (21%) in trials of prostacyclin analogs. Patients with CTD-associated PAH were more likely to be enrolled in a trial of ERAs compared to patients with idiopathic PAH (Table 1).

Adverse events

At least 1 AE occurred in 1,944 patients (82%) overall. Among patients with idiopathic PAH, 1,346 (81%) developed an AE, and among those with CTD-associated PAH, 598 (84%) experienced an AE. The median number of AEs experienced by an individual patient was similar between CTD-associated PAH and idiopathic PAH (Table 2). The most common AEs included infection, headache, musculoskeletal issues, edema, and rash (Table 3).

Patients with CTD-associated PAH in the active treatment group compared to the placebo group were more likely to have AEs than were patients with idiopathic PAH in the active treatment group compared to the placebo group (odds ratio [OR] 1.57, 95% confidence interval [95% CI] 1.00–2.47 versus OR 0.94, 95% CI 0.69–1.26; P for interaction = 0.061) (Figure 1). The meta-analysis evaluating the pooled estimates of interaction effect for occurrence of AEs across studies showed there was no statistically significant heterogeneity between 7 of the 10 trials ($I_2 = 0.0\%$, $P = 0.82$) (Figure 2). Three of the trials could not be analyzed in the test for heterogeneity because of the low number of events.

The treatment-by-diagnosis interaction was not significant for all other secondary AE outcomes, including edema, dyspnea, and infection. These secondary outcomes were then evaluated for an association with diagnosis (without effect modification by treatment). There was no difference in the rate of AEs in patients with CTD-associated PAH compared to those with idiopathic PAH (incidence rate ratio 1.08, 95% CI 0.96–1.21; $P = 0.18$). When we examined the 10 most common AEs, we found that patients with CTD-associated PAH had a significantly higher occurrence of infection (OR 1.65, 95% CI 1.31–2.08; $P < 0.001$) and bleeding (OR 1.49, 95% CI 1.08–2.06; $P = 0.021$), in analyses adjusted for age, race, sex, treatment, study, BMI, baseline 6-minute walk distance, baseline WHO functional class, baseline hemodynamics (cardiac index, mean pulmonary arterial pressure, right atrial pressure), and baseline laboratory values (creatinine and hemoglobin levels) (Table 3).

There was no interaction between treatment and diagnosis subgroup (SSc-associated PAH versus idiopathic PAH) for either the primary outcomes or any of the secondary outcomes (P for interaction>0.10 for all comparisons). No significant interactions were found in the subgroup analysis stratified by drug type—ERA, PDE5 inhibitors, and prostacyclin analogs (data not shown).

Serious adverse events

At least 1 SAE occurred in 371 patients (16%) overall, of whom 236 with idiopathic PAH (14%) and 135 with CTD-associated PAH (19%) had at least 1 SAE (Table 2). The most common SAEs included congestive heart failure, infection, worsening PAH, bleeding, and dyspnea. There was no difference in treatment-related SAEs in CTD-associated PAH compared to idiopathic PAH (P for interaction = 0.11) (Figure 3). When the relationship between diagnosis (CTD-associated PAH versus idiopathic PAH) alone and occurrence of an SAE was examined, patients with CTD-associated PAH overall were more likely to develop an SAE during the trial period compared to patients with idiopathic PAH, independent of treatment assignment, although the difference was not statistically significant (OR 1.30, 95% CI 0.99–1.72; $P = 0.061$). Therefore, SAEs occurred more often in patients with CTD-

associated PAH than in patients with idiopathic PAH, and this difference was unrelated to therapy. There was no difference in the rate of SAEs between patients with CTD-associated PAH and those with idiopathic PAH (incidence rate ratio 1.17, 95% CI 0.82–1.66; $P = 0.38$).

We found no significant differences in the effect of treatment on occurrence of an SAE between patients with SSc-associated PAH and those with idiopathic PAH (P for interaction = 0.23). Secondary analyses of SAEs stratified by drug type found no differences in treatment-related SAEs between the 2 diagnoses within the 3 individual drug types (data not shown).

Risk of treatment discontinuation due to adverse events/serious adverse events

Among the 1,944 patients who experienced an AE, 140 (7%) had to discontinue the study drug due to the AE. There was no treatment-by-diagnosis interaction in terms of discontinuation of the drug due to an AE, indicating that the risk of treatment discontinuation among patients receiving active treatment compared to those receiving placebo was not influenced by diagnosis of CTD-associated PAH or idiopathic PAH, even after adjusting for age, sex, baseline 6-minute walk distance, and baseline pulmonary vascular resistance (P for interaction = 0.27). Furthermore, neither of the 2 diagnoses (OR 0.84, 95% CI 0.56–1.25; $P = 0.39$) nor treatment assignment (OR 0.86, 95% CI 0.60–1.22; $P = 0.39$) was independently associated with treatment discontinuation due to AEs, in analyses adjusted for all potential confounders.

Among the 371 patients who developed an SAE, 78 (21%) had to discontinue the study drug due to the SAE. The diagnosis did not modify treatment-related discontinuations of the study drug due to an SAE (P for interaction = 0.15). Furthermore, discontinuation of treatment was not associated with diagnosis (OR 0.72, 95% CI 0.40–1.29; $P = 0.28$) or treatment (OR 0.64, 95% CI 0.38–1.09; $P = 0.10$).

DISCUSSION

This study shows that the risk of treatment-related AEs is higher in participants of clinical trials diagnosed as having CTD-associated PAH than in participants with idiopathic PAH. This indicates that patients randomized to receive active therapy were more likely to develop an AE compared to those receiving placebo if they had CTD-associated PAH than if they had idiopathic PAH. Despite the higher risk of AEs in patients with CTD-associated PAH, the rate of drug discontinuation due to an AE or SAE was not different between the 2 groups.

Patient characteristics were similar to those of patients from prior studies (9,11,13,18,46,47). Patients with CTD-associated PAH were older and were more often female compared to patients with idiopathic PAH. Baseline hemodynamic measurements were less affected in CTD-associated PAH compared to idiopathic PAH, which is consistent with prior published studies (12,13,18). These differences were accounted for in the analyses, so that our findings are independent of these underlying differences. Although patients with CTD-associated PAH had less severely altered hemodynamics, the baseline 6-minute walk distance was significantly lower in those with CTD-associated PAH. An explanation for this discrepant

finding may be attributed to other features of disease, such as pericardial or myocardial complications, which may cause the poorer exercise capacity in CTD-associated PAH (11,13,18). In addition, the 6-minute walk distance may be disproportionately affected by concurrent joint disease, muscle wasting, and poor overall health in CTD-associated PAH (48–51).

The higher risk of AEs in patients with CTD may be explained by the complex multiorgan involvement of their underlying systemic disease, as well as by the immunosuppressive therapies required for treatment. The presence of cytopenia, most often due to the use of immunomodulating agents as well as to the presence of intrinsic immune dysfunction, may predispose patients with CTD to infections. Vascular malformations and clotting abnormalities (e.g., thrombocytopenia) may contribute to bleeding tendencies. Immunosuppressive therapies used to treat CTDs are associated with toxicities, and potentially unknown drug interactions with therapies for PAH may have occurred. Moreover, gastrointestinal disease seen in CTDs (especially in those with SSc-associated CTD) can cause malabsorption, which may affect the bioavailability and drug concentration of these advanced vasodilator therapies; however, decreased absorption in patients with CTD-associated PAH would be expected to bias the results toward the null. Notably, there was not a higher occurrence of dyspnea in patients with CTD-associated PAH, which may have been expected given the higher prevalence of pulmonary venoocclusive disease (PVOD)—thereby conferring a higher risk of pulmonary edema in the active therapy group—in patients with CTD (52,53). Therefore, it is likely that clinically apparent PVOD was uncommon in this population of patients with CTD.

Notably, the higher occurrence of treatment-related AEs in patients with CTD-associated PAH did not translate into an increased risk of drug discontinuation due to an AE. This may indicate that treatment-related AEs in patients with CTD-associated PAH, although greater in number, were not severe enough to warrant treatment discontinuation. Alternatively, it may be possible that there were not enough events to detect a difference (inadequate power).

Understanding the heterogeneity of treatment effects within subgroups of patients has become a major research priority (54). This is the first study to evaluate issues of safety in patients with CTD-associated PAH compared to patients with idiopathic PAH within randomized controlled trials. We found that patients with CTD-associated PAH assigned to active treatment are more likely to experience AEs compared to those receiving placebo, whereas patients with idiopathic PAH had no difference in the occurrence of AEs between the treatment and placebo groups. Our study used individual patient data from 10 randomized controlled trials, which allowed us to examine patient subgroups, adjusted for potential confounders, and utilize interaction terms. Furthermore, the power to detect differences was substantially increased by pooling data from multiple studies.

Drug development programs may choose to more comprehensively distinguish between patients with CTD-associated PAH and those with idiopathic PAH, and to prospectively study differential treatment responses and toxicity profiles as well as potential drug interactions. In addition, analysis of AEs and SAEs in clinical trials may warrant stratification by diagnosis to determine whether AEs are occurring mostly in CTD-

associated PAH. This study found no evidence of an increased risk of drug discontinuation due to an AE between patients with CTD-associated PAH and those with idiopathic PAH. Because patients with CTD-associated PAH have a higher risk of AEs, anticipating potential AEs and performing appropriate monitoring could minimize the occurrence and impact of AEs on patients, improving their quality of life.

Several limitations of this analysis are also important to consider. Misclassification bias may have occurred if patients with CTD were incorrectly diagnosed. A diagnosis of CTD was based on physician reporting, and standardized classification criteria were not used. However, patient characteristics, such as age, sex, race, and baseline hemodynamics, as well as differences between patients with CTD-associated PAH and those with idiopathic PAH, were similar to that reported in previous studies (11,18). In addition, we would expect that patients with CTD would be more likely misdiagnosed as having idiopathic PAH, which would bias toward the null hypothesis; therefore, the true differences between CTD-associated PAH and idiopathic PAH may be even larger than has been shown in this study.

Second, reporting bias may have occurred, since clinicians were not blinded with regard to the diagnosis and therefore may have been more prone to report AEs in those with a CTD diagnosis; however, allocation of treatment was masked, and therefore reporting bias would not explain the significant treatment-by-diagnosis interactions. The patients studied were enrolled in clinical trials and may differ from other populations, affecting generalizability. The relatively short length of followup may have limited the examination of certain AEs in these trials. Furthermore, these trials were not designed to examine differences in AEs between CTD-associated PAH and idiopathic PAH, and therefore unmeasured and residual confounders may exist; however, if proper randomization occurred, comparison of treatment and placebo groups within diagnoses should not be affected.

Another limitation is the possibility of Type I error. Selection of a higher alpha level has been recommended for studies of effect modification, given the greater power needed to assess interactions (45). However, rather than relying solely on P values, examination of estimates and confidence intervals (which are better at conveying magnitude and precision) is generally favored (55). There is clearly heterogeneity between the diagnostic groups.

No between-study heterogeneity was found with formal testing. Although 3 of the studies (the BREATHE-1, STRIDE-1 [Sitaxsentan to Relieve Impaired Exercise 1], and treprostinil studies) could not be included in the test for heterogeneity and in the formal meta-analysis (because of the low number of observations), these studies had a similar study design and similar inclusion/exclusion criteria, and therefore inclusion of the 3 trials would be unlikely to significantly change the results. In addition, a prior analysis that did include these 3 trials showed minimal statistical heterogeneity (P for heterogeneity = 0.99) (56). Furthermore, unmeasured confounders, such as concomitant medications used and existing comorbidities, also limit the interpretation of the data.

In conclusion, this study found that among patients enrolled in therapeutic clinical trials, more treatment-related AEs occurred in patients with CTD-associated PAH compared to those with idiopathic PAH, but no difference in the occurrence of SAEs or in treatment

discontinuation due to an AE/SAE was observed. These findings suggest that the overall benefit of advanced therapies for PAH may be attenuated by the greater frequency of AEs. The results nevertheless support the continued enrollment of patients with CTD-associated PAH into clinical trials of therapies for PAH.

Acknowledgments

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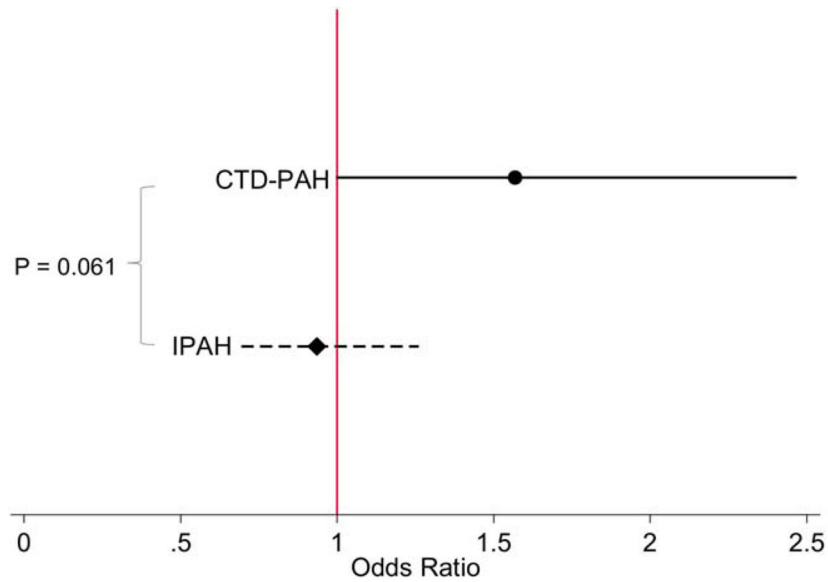
Figure 1.
Odds ratios for adverse events (AEs) in patients assigned to the active treatment group as compared to the placebo group, stratified by diagnosis (connective tissue disease–associated pulmonary arterial hypertension [CTD-PAH] and idiopathic PAH [IPAH]). Odds ratios are shown with 95% confidence intervals. Compared to patients with IPAH, patients with CTD-associated PAH were more likely to experience an AE if assigned to active treatment versus placebo. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39220/abstract.
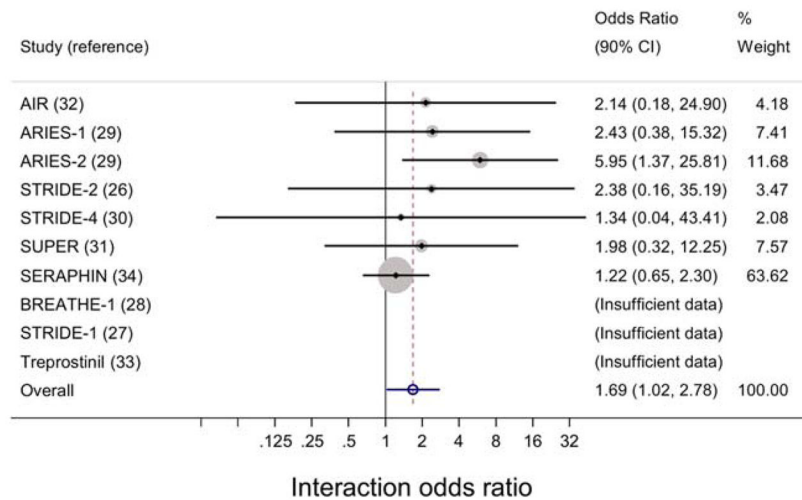
Figure 2.
Interaction effect estimates from individual studies and from meta-analysis of pooled studies to assess the impact of diagnosis-by-treatment interaction on adverse events in patients with connective tissue disease–associated pulmonary arterial hypertension and those with idiopathic pulmonary arterial hypertension. Forest plots show the odds ratios with 90% confidence intervals (90% CIs) for the diagnosis-by-treatment interactions and occurrence of adverse events. Three studies (the BREATHE-1 [Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy for Pulmonary Arterial Hypertension 1], STRIDE-1 [Sitaxsentan to Relieve Impaired Exercise 1], and treprostinil studies) had an insufficient number of events and therefore could not be analyzed ($I_2 = 0.0\%$, $P = 0.82$). AIR = Aerosolized Iloprost Randomized Study; ARIES-1 = Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1; SUPER = Sildenafil Use in Pulmonary Arterial Hypertension; SERAPHIN = Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39220/abstract.
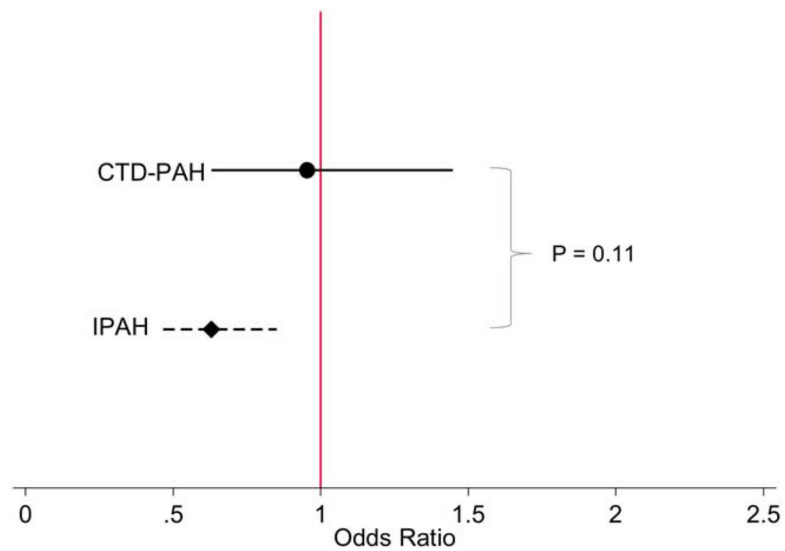
Figure 3.
Odds ratios for serious adverse events (SAEs) in patients assigned to the active treatment group as compared to the placebo group, stratified by diagnosis (connective tissue disease–associated pulmonary arterial hypertension [CTD-PAH] and idiopathic PAH [IPAH]). Odds ratios are shown with 95% confidence intervals. There was no significant difference in the occurrence of treatment-related SAEs between the CTD-associated PAH and idiopathic PAH groups. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39220/abstract.

Table 1

Characteristics of the study participants[*]

	CTD-associated PAH			Idiopathic PAH (n = 1,654)	P, all CTD-associated PAH vs. idiopathic PAH
	All (n = 716)	SSc-associated PAH (n = 407)	Non–SSc-associated PAH (n = 309)		
Age, years	53 ± 14	59 ± 11	45 ± 14	46 ± 15	<0.001
Female sex, %	89	88	90	73	<0.001
Race, %					0.39
White	71	88	49	73	
Black	5	4	6	4	
Other	25	8	45	23	
Body mass index, kg/m^2	26 ± 6	27 ± 6	26 ± 6	28 ± 7	<0.001
WHO functional class, %					0.18
I–II	47	37	59	44	
III–IV	53	63	41	56	
Baseline hemodynamics					
Right atrial pressure, mm Hg	8.0 ± 5.0	8.3 ± 4.9	7.7 ± 5.0	9.6 ± 5.8	<0.001
Mean pulmonary arterial pressure, mm Hg	46 ± 12	45 ± 13	48 ± 12	56 ± 16	<0.001
Cardiac index, liters/minute/m^2	2.5 ± 0.8	2.5 ± 0.8	2.5 ± 0.8	2.3 ± 0.8	<0.001
Pulmonary capillary wedge pressure, mm Hg	9 ± 4	10 ± 3	9 ± 3	9 ± 4	0.70
Pulmonary vascular resistance, Wood units	10.2 ± 6.2	9.6 ± 6.4	10.9 ± 5.9	13.3 ± 7.8	<0.001
Baseline 6-minute walk distance, meters	336 ± 93	322 ± 92	353 ± 91	347 ± 89	<0.001
Drug class, %					0.021
Endothelin receptor antagonists	71	72	69	67	
Phosphodiesterase 5 inhibitors	12	13	11	13	
Prostacyclin analogs	17	16	20	22	

[*] Except where indicated otherwise, values are the mean ± SD.

CTD-associated PAH = connective tissue disease–associated pulmonary arterial hypertension; SSc = systemic sclerosis; WHO = World Health Organization.

Table 2

Adverse events (AEs) and serious adverse events (SAEs) by diagnosis [*]

		CTD-associated PAH			
	All (n = 716)	SSc-associated PAH (n = 407)	Non–SSc-associated PAH (n = 309)	Idiopathic PAH (n = 1,654)	*P*, all CTD-associated PAH vs. idiopathic PAH
AE					
Occurrence of at least 1 AE, %	84	87	79	81	0.20
AEs per person, median (IQR) no.	3 (1–7)	3 (1–7)	3 (1–6)	3 (1–6)	0.87
SAE					
Occurrence of at least 1 SAE, %	19	20	17	14	<0.001
SAEs per person, %					<0.001
0	81	80	83	86	
1	14	14	13	9	
>1	5	6	4	5	

[*] CTD-associated PAH = connective tissue disease–associated pulmonary arterial hypertension; SSc = systemic sclerosis; IQR = interquartile range.

Table 3

Risk of the 10 most common adverse event types in patients with CTD-associated PAH compared to patients with idiopathic PAH[*]

Outcome	Odds ratio (95% CI) for CTD-associated PAH vs. idiopathic PAH	P
Infection	1.65 (1.31–2.08)	<0.001
Headache	0.85 (0.65–1.13)	0.26
Musculoskeletal	1.13 (0.87–1.48)	0.36
Edema	1.12 (0.85–1.48)	0.42
Rash	0.89 (0.62–1.29)	0.54
Bleeding	1.49 (1.08–2.06)	0.021
Nausea/vomiting	1.10 (0.78–1.54)	0.59
Dizziness	1.09 (0.78–1.52)	0.62
Cough	0.99 (0.66–1.49)	0.98
Dyspnea	1.33 (0.91–1.93)	0.14

[*] Odds ratios with 95% confidence intervals (95% CIs) were determined in analyses adjusted for age, sex, race, treatment (drug versus placebo), study, body mass index, baseline 6-minute walk distance, baseline World Health Organization functional class, baseline hemodynamics (cardiac index, mean pulmonary arterial pressure, right atrial pressure), and baseline laboratory values (creatinine and hemoglobin levels). CTD-associated PAH = connective tissue disease–associated pulmonary arterial hypertension.