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BRIEF REPORT

Effect of Ambrisentan Treatment on Exercise-Induced Pulmonary Hypertension in Systemic Sclerosis: A Prospective Single-Center, Open-Label Pilot Study

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Objective. **Exercise-induced pulmonary hypertension (ePH) may represent an early, clinically relevant phase in the spectrum of pulmonary vascular disease. The purpose of this pilot study was to describe the changes in hemodynamics and exercise capacity in patients with systemic sclerosis (SSc) spectrum–associated ePH treated with open-label daily ambrisentan.**

Methods. **Patients were treated with ambrisentan, 5 mg or 10 mg once daily, for 24 weeks. At baseline and 24 weeks, patients with SSc spectrum disorders exercised in a supine position, on a lower extremity cycle ergometer. All patients had normal hemodynamics at rest. We defined baseline ePH as a mean pulmonary artery pressure of >30 mm Hg with maximum exercise and a transpulmonary gradient (TPG) of >15 mm Hg. The primary end point was change in pulmonary vascular resistance (PVR) with exercise. Secondary end points included an improvement from baseline in 6-minute walking distance, health-related quality of life assessments, and cardiopulmonary hemodynamics.**

Results. **Of the 12 enrolled patients, 11 completed the study. At 24 weeks there were improvements in mean exercise PVR (85.8 dynes × second/cm^5; $P = 0.003$) and mean distance covered during 6-minute walk (44.5 meters; $P = 0.0007$). Improvements were also observed in mean exercise cardiac output (1.4 liters/minute; $P = 0.006$), mean pulmonary artery pressure (−4.1 mm Hg; $P = 0.02$), and total pulmonary resistance (−93.0 dynes × seconds/cm^5; $P = 0.0008$). Three patients developed resting pulmonary arterial hypertension during the 24 weeks.**

Conclusion. **Exercise hemodynamics and exercise capacity in patients with SSc spectrum–associated ePH improved over 24 weeks with exposure to ambrisentan. Placebo-controlled studies are needed to confirm whether this is a drug-related effect and to determine optimal therapeutic regimens for patients with ePH.**

Despite fewer severe hemodynamic abnormalities, patients with systemic sclerosis (SSc) pulmonary arterial hypertension (PAH) tend to have a poorer prognosis compared to those with other types of associated PAH or idiopathic PAH (1). Survival is related, in part, to the degree of hemodynamic compromise, with key variables, including resting pulmonary vascular resistance (PVR), stroke volume index, and pulmonary arterial capacitance, all strongly associated with mortality (2). In addition, data from a large registry in the UK show that one-fifth of SSc patients with exercise-induced pulmonary hypertension (PH) developed resting PAH after ~2.3 years (3).

We recently reported on 4 potential hemodynamic phenotypes of SSc spectrum disorders that

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emerge in patients exercising with catheterization of the right side of the heart, including normal, exercise-induced pulmonary venous hypertension (ePVH), exercise out of proportion pulmonary hypertension (eoPH), and exercise-induced pulmonary hypertension (ePH) (4). Our findings and those of others suggest that SSc patients with a borderline resting mean pulmonary artery pressure (mPAP) of 21–24 mm Hg and/or a PVR of ≥160 dynes × seconds/cm^5 at baseline are at higher risk of developing progressive pulmonary vascular disease (4,5). A hemodynamic evaluation of SSc-associated PH patients during exercise may allow for earlier diagnosis, initiation of appropriate therapy, and perhaps, a more favorable outcome (6). In this 24-week uncontrolled, open-label study, we assessed the effects of open-label ambrisentan on cardiopulmonary hemodynamics during exercise, exercise capacity, and the safety and tolerability of ambrisentan in patients with SSc-associated ePH.

PATIENTS AND METHODS

This prospective study involved 12 patients with SSc spectrum disorders who underwent exercise with catheterization of the right side of the heart at a single university hospital. This data collection was approved by the University of California, Los Angeles Institutional Review Board.

We identified patients with an SSc spectrum disease (either limited cutaneous SSc, diffuse cutaneous SSc, or an overlap syndrome), based on the American College of Rheumatology classification criteria (7). Disease duration was defined as the time since the first non–Raynaud's phenomenon symptom attributable to SSc. Patients of either sex, without limitations on disease duration, were eligible for the study.

Based on prior published recommendations, patients underwent right-sided heart catheterization if they had dyspnea and at least 1 of the following: a resting Doppler echocardiography–estimated right ventricular systolic pressure of ≥30 mm Hg (8), a 15% decline in diffusing capacity for carbon monoxide (DLco) (% of predicted) during the preceding 2 years, a DLco of ≤60%, or a forced vital capacity (FVC):DLco ratio of >1.4% predicted (9,10). Patients with moderate-to-severe pulmonary fibrosis were included in the analysis. The degree of fibrosis on high-resolution computed tomography (CT) of the chest was scored by a thoracic radiologist (FA), who was blinded with regard to clinical and hemodynamic information, using a grading system based on a modified Likert scale (0 = absent, 1 = 1–5%, 2 = 6–25%, 3 = 26–50%, 4 = 51–75%, 5 = 76–100%) (11). Using results of Doppler echocardiography, we excluded patients who had evidence of significant resting systolic dysfunction (ejection fraction <50%) and/or diastolic dysfunction (more than mild) of the left side of the heart.

Study protocol. The majority of patients were initially started on 10 mg of ambrisentan daily; however, titration was allowed based on physician discretion. The drug was provided by Gilead Sciences for the duration of the study. Safety laboratory testing was performed on a monthly basis, including blood tests for determination of liver and renal function and complete blood cell counts. Due to a high incidence of edema (especially lower extremity) that was successfully managed by daily or intermittent administration of diuretics, 2 patients were treated with 5 mg of ambrisentan daily for the first month, after which the dosage was increased to 10 mg daily. Daily ambrisentan was continued for 24 weeks. The patients were asked to return 4 weeks after discontinuing the drug, for a safety assessment.

Health-related quality of life (HRQOL) measures. HRQOL was assessed using the Short Form 36 (SF-36) health survey, version 2 (12), the Health Assessment Questionnaire (HAQ) disability index (DI) (13), and the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) index (14).

Definition of PH. PH was defined as a resting mPAP of ≥25 mm Hg with right-sided heart catheterization; PAH was defined as PH in addition to pulmonary capillary wedge pressure (PCWP) of ≤15 mm Hg (15). A hemodynamic evaluation was performed during maximal exercise in patients without resting PH. We defined ePH as an mPAP of >30 mm Hg, PCWP of ≤18 mm Hg (16), and a transpulmonary gradient (TPG) of ≥15 mm Hg (17), where TPG = mPAP – PCWP. We defined ePVH as an mPAP of >30 mm Hg, PCWP of >18 mm Hg, and a TPG of <15 mm Hg. We defined eoPH as an mPAP of >30 mm Hg, PCWP of >18 mm Hg, and a TPG of ≥15 mm Hg (4). Our hypothesis was that SSc patients with normal exercise physiology and ePVH have a different pathophysiology compared to patients with pulmonary vascular disease (ePH and eoPH). Since patients with ePH and eoPH are otherwise hemodynamically indistinguishable during exercise, they may be at risk of developing progressive pulmonary vascular disease and were included in this analysis (4), while the normal and ePVH groups were excluded.

Resting and exercise right-sided heart catheterization protocol. Hemodynamic evaluation was performed with patients at rest and during exercise. Exercise was performed with the patient in a supine position, using a lower extremity cycle ergometer according to our standard protocol as previously described (4).

Statistical analysis. Continuous variables are reported as the mean ± SD, while categorical variables are reported as the percentage of patients. The statistical significance of changes in scores from baseline was assessed using either Student's paired *t*-test or Wilcoxon's rank sum test depending on the distributional properties of each variable.

RESULTS

Patient characteristics. Twelve patients with SSc spectrum disorders met inclusion criteria and agreed to participate in the study. At baseline, the mean ± SD distance covered during the 6-minute walk test was 404.7 ± 75.4 meters. The majority of patients were women (91.6%) and white (33.3%) or African American (33.3%); the mean ± SD age was 47.6 ± 19.4 years

Table 1. Baseline characteristics of the 12 study patients with SSc spectrum disorders*

Age, years	47.6 ± 19.4
Women, no. (%)	11 (91.6)
Race, no. (%)	
White	4 (33.3)
African American	4 (33.3)
Asian	1 (8.3)
Hispanic	3 (25)
Type of SSc, no.	
Limited	8
Diffuse	3
Overlap	1
RP duration, years	12.3 ± 9.4
Non-RP duration, years	8.0 ± 4.1
WHO functional class II, no. (%)	12 (100)
FVC, % predicted	69.8 ± 19.4
DLco, % predicted	58.5 ± 21.1
FVC:DLco	1.24 ± 0.26
Pulmonary fibrosis (HRCT), no. (%)	
Grade 0	2 (16.6)
Grade 1	7 (31.8)
Grade 2	2 (16.6)
Grade 3	1 (8.3)
Grade 4	0 (0)
LVEF on echocardiography, %	55.8 ± 4.7
Diastolic dysfunction, no. (%)	0 (0%)
Estimated RVSP, mm Hg	32.1 ± 5.1
RV dilation, no. (%)	
None	5 (41.6)
Mild	7 (58.3)
Pericardial effusion, no. (%)	0 (0)
CT fibrosis score	1.8 ± 1.1

* Except where indicated otherwise, values are the mean ± SD. SSc = systemic sclerosis; RP = Raynaud's phenomenon; WHO = World Health Organization; FVC = forced vital capacity; DLco = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure; RV = right ventricle.

(Table 1). Eight patients (66.7%) had limited cutaneous SSc, 3 (25%) had diffuse cutaneous SSc, and 1 (8.3%) had an overlap syndrome. The mean FVC was 69.8%, the mean DLco was 58.5%, and the mean FVC:DLco ratio was 1.24. Two patients had an FVC of <60%, and their fibrosis scores on CT chest scans were grades 3 and 4, respectively. Patients had mild functional disability (mean HAQ DI 0.51), and their SF-36 physical component summary score was 1.3 SD below the average for the US general population. CAMPHOR function scores (mean 8.9) were somewhat better than those found in a US population study (14), whereas symptom scores (mean 10.5) as assessed by CAMPHOR were somewhat worse.

Resting hemodynamics. Resting cardiopulmonary hemodynamics at baseline and at week 24 are reported in Table 2. No significant changes in mPAP, PCWP, pulmonary artery O_2 saturation (Svo_2), PVR, total pulmonary resistance (TPR), and heart rate were seen between baseline and study end. A significant improvement in stroke volume index and stroke volume was seen at week 24 compared to baseline. Three patients had developed resting PAH (15) (mPAP of >25 mm Hg at week 24). Of those patients, 2 had an increase in resting PVR and TPR and a decline in resting stroke volume, stroke volume index, and pulmonary arterial capacitance (stroke volume/pulse pressure [SV/PP]). The remaining patient exhibited a decline in resting PVR and TPR, and an increase in resting stroke volume, stroke volume index, and SV/PP.

Exercise hemodynamics. Cardiopulmonary hemodynamics during exercise significantly improved from baseline to week 24 (Table 2). During exercise, mean ± SD values decreased as follows: mPAP 41.5 to 37.4 (P = 0.02), PVR 247.1 to 161.3 (P = 0.003), TPR 405.7 to 312.7 (P = 0.0008) (Table 2). Improvement in cardiac output, stroke volume, and stroke volume index was also seen. No change in PCWP or Svo_2 was observed. Interestingly, a significant reduction in peak heart rate was seen at week 24 compared to baseline (mean 131.5 versus 119.2; P = 0.006).

Exercise capacity. After 24 weeks, 6-minute walking distance significantly improved, by a mean ± SD of 44.5 ± 10.3 meters. In 1 patient, who developed

Table 2. Hemodynamic variables*

	Baseline (n = 12)	Posttreatment (n = 11)	P
Resting, mean ± SD			
mPAP, mm Hg	20.9 ± 2.9	22.2 ± 5.8	0.65
CO, liters/minute	4.8 ± 0.9	5.9 ± 0.7	0.01
PCWP, mm Hg	11.3 ± 3.5	11.9 ± 2.3	0.58
Svo_2, %	71.1 ± 4.1	71.4 ± 6.1	0.58
PVR, dynes × seconds/cm^5	169.1 ± 67.7	138.9 ± 65.4	0.12
TPR, dynes × seconds/cm^5	358.7 ± 81.9	298.9 ± 81.6	0.12
HR, beats per minute	81.1 ± 17.2	78.8 ± 14.9	0.52
SV, ml	60.2 ± 9.9	78.4 ± 16.0	0.003
SVI, ml/m^2	33.7 ± 5.6	43.5 ± 10.7	0.006
Exercise, mean ± SD			
mPAP, mm Hg	41.5 ± 5.3	37.4 ± 8.3	0.02
CO, liters/minute	8.4 ± 1.6	9.8 ± 2.2	0.006
PCWP, mm Hg	16.5 ± 5.2	17.8 ± 3.5	0.88
Svo_2, %	51.2 ± 8.0	51.4 ± 5.6	0.83
PVR, dynes × seconds/cm^5	247.1 ± 69.1	161.3 ± 66.7	0.003
TPR, dynes × seconds/cm^5	405.7 ± 73.8	312.7 ± 82.9	0.0008
HR, beats per minute	131.5 ± 19.9	119.2 ± 18.7	0.006
SV, ml	62.7 ± 13.4	80.7 ± 17.3	0.002
SVI, ml/m^2	35.0 ± 7.4	44.5 ± 9.3	0.002

* mPAP = mean pulmonary artery pressure; CO = cardiac output; PCWP = pulmonary capillary wedge pressure; Svo_2 = pulmonary artery O_2 saturation; PVR = pulmonary vascular resistance; TPR = total pulmonary vascular resistance; HR = heart rate; SV = stroke volume; SVI = stroke volume index.

resting PH, exercise capacity declined by 37 meters. In 2 other patients, who also developed resting PH, the 6-minute walking distance improved by 53 meters. Eight of 11 patients (72.7%) had a ≥10% improvement in distance covered during the 6-minute walking test at 24 weeks compared to baseline. In the 6 patients who discontinued ambrisentan after study completion at week 24, distance covered during a 6-minute walking test on week 28 declined by 20.5 ± 30.5 meters from week 24 (data not shown). World Health Organization (WHO) functional class was maintained through 6 months in the majority of the group. One patient improved and 1 patient worsened by 1 functional class.

HRQOL assessments. Improvements in the results obtained with the 3 HRQOL instruments were not significant (data not shown). The improvement in the SF-36 physical component summary score (11.7 SD) was greater than the minimally important difference. The change in SF-36 mental component summary score and HAQ DI did not reach minimally important difference estimates.

Patients with an FVC of ≥60% versus those with an FVC of <60%. Two patients (16.6%) had an FVC of <60%, while 10 (83.3%) had an FVC of ≥60%. Patients with an FVC of <60% had a fibrosis score of ≥3 on CT scan. There were significant differences between those with an FVC of <60% and those with an FVC of ≥60% in mean resting PVR (240.3 dynes × seconds/cm^5 versus 116.4 dynes × seconds/cm^5, respectively) and resting TPR (420.3 dynes × seconds/cm^5 versus 271.9 dynes × seconds/cm^5, respectively). There were no differences in the hemodynamic parameters during exercise, including mean PVR, TPR, cardiac output, mPAP, and maximum heart rate.

Exercise out of proportion PH versus exercise-induced PH. Three patients met criteria for eoPH; the remainder were classified as having ePH. There were no significant differences between these 2 groups in regard to exercise hemodynamics, HRQOL, exercise capacity, and adverse events.

Adverse events. Adverse events were common in this 24-week, open-label trial (Table 3). Common adverse events included lower extremity edema, nasal congestion, and upper respiratory symptoms. One patient developed intractable lower extremity edema and subsequently withdrew from the study at week 4; her edema resolved thereafter. Nasal congestion in conjunction with upper respiratory symptoms was common (41.6%) and usually self-limited. None of the patients developed serum aminotransferase concentrations >3 times the upper limit of normal. One patient developed alanine aminotransferase levels that were 2 times the upper limit of normal; however, levels normalized on repeat analysis without dose adjustment.

Table 3. Adverse events during ambrisentan treatment*

Upper respiratory symptoms	2
Nasal congestion	5
Severe constipation	1
Severe joint and body pain	1
Elevated levels on LFT†	1
Edema‡	5
Headaches	1
Tinea corporis	1
Allergic reaction§	1
Bronchoalveolar carcinoma	1
Increased fecal incontinence	1
Pulled back muscle	1

* Values are the number of events; in some patients, >1 adverse event occurred.
† Results on liver function tests (LFT) were elevated to <3 times the upper limit of normal.
‡ One patient discontinued treatment after 4 weeks.
§ Swollen eyes and itching skin.

One patient was diagnosed as having nonmucinous bronchoalveolar carcinoma after completion of the study, which was determined not to be related to the study drug. After a successful lobectomy, the patient is doing well 2 years later. Less common adverse events included constipation, body pain, and headaches. Numbness and rash at the catheter insertion site after catheterization of the right side of the heart occurred in 2 patients, without further sequelae.

DISCUSSION

Exercise-induced PH in patients with SSc may be an abnormal hemodynamic response and part of a continuum from normal hemodynamics to resting PH. We previously reported that patients diagnosed as having ePH or eoPH may be at risk of developing progressive pulmonary vascular disease (4), and as such, we included these patients in this study.

To our knowledge, this is the first open-label pilot study of the clinical efficacy and safety of an endothelin receptor antagonist for the treatment of patients with SSc spectrum–associated ePH. Our results suggest that long-term oral administration of ambrisentan may be associated with significant improvement in cardiopulmonary hemodynamics during exercise and exercise capacity (6-minute walking distance) in these patients. These improvements included a significant decrease in PVR, TPR, and mPAP during exercise. Additional improvements in cardiac output, stroke volume, and stroke volume index were seen.

In SSc patients with PAH, PVR, stroke volume index, and pulmonary arterial capacitance (SV/PP) are strong predictors of mortality (2). However, there is a paucity of data regarding longitudinal followup in patients with ePH; as such, predictors of progression and survival have not been determined. Condliffe et al reported survival in 42 SSc patients with ePH, of whom 19% progressed to having resting PAH within 2.3 years; of those, 5 died secondary to complications of right ventricular dysfunction (3). Tolle et al recently described exercise PAH as an intermediate phenotype between normal and resting PAH assessed by cardiopulmonary exercise and hemodynamic end points in symptomatic non-SSc patients (18). Furthermore, a recent report described an association between exercise hemodynamics (mPAP) and exercise capacity (6-minute walking distance and peak maximum $\dot{V}O_2$ [$\dot{V}O_2$max]) in an SSc cohort without resting PAH (5). Additional investigation is needed to determine the appropriate indicators of maximum effort and the prognostic value of $\dot{V}O_2$max and 6-minute walking distance in SSc patients with ePH.

In our study, 3 patients (25%) developed resting PH (mPAP >25 mm Hg) despite receiving ambrisentan. Surprisingly, only 1 of the 3 patients had a decline in 6-minute walking distance accompanied by a worsening functional class. The remaining 2 patients had improved exercise capacity and unchanged functional class, suggesting a possible discordance between hemodynamics (mPAP) and 6-minute walking distance.

Interestingly, 2 of the 3 patients who progressed to develop resting PH had an FVC of <60%, whereas the rest of the cohort had an FVC of >60%. Patients with an FVC of <60% associated with significant interstitial lung disease are excluded from WHO class I, and the associated pulmonary vasculopathy is often considered to be a manifestation of the underlying interstitial lung disease and/or hypoxia (15). Nevertheless, SSc-associated PH with pulmonary fibrosis also portends a poorer prognosis than isolated SSc-associated PAH (1). We suggest that this specific population should be evaluated in a longitudinal manner.

The Dana Point guidelines recommended that the exercise criterion of an mPAP value of >30 mm Hg to designate ePH should be reassessed, given both the marked age dependency of the normal mPAP threshold on exercise and the paucity of robust data supporting its clinical relevance (15,19). In addition, these guidelines highlighted the importance of close monitoring of patients with a resting mPAP of 21–24 mm Hg (15). In our study, the mean age was 47.6 years, and 9 of 12 patients had a resting mPAP of 21–24 mm Hg.

Common adverse events seen during our clinical trial have been previously reported in clinical trials of ambrisentan, and they were anticipated. Adverse events included lower extremity edema, nasal congestion, and upper respiratory symptoms. The majority of these adverse events were managed by either decreasing the dose of ambrisentan or temporarily discontinuing ambrisentan. Persistent lower extremity edema was typically managed with the addition of a daily oral loop diuretic.

There were a few adverse events that were surprising. One patient, who had minimal fibrosis at baseline, developed a new bronchoalveolar carcinoma, which was detected on a high-resolution CT chest scan at week 24. This was judged not to be related to the study drug. Currently, there are no reports of carcinogenesis in humans attributable to ambrisentan (according to the package label). Ambrisentan-related carcinogenicity has been described in studies of male rats receiving 8–140 times the maximum recommended dose (in mg/m^2) for humans (package label).

Although our results are promising, they are restricted by the small number of patients, the single-center design of the trial, the absence of a placebo group, inclusion of patients with pulmonary fibrosis, and the absence of simultaneous cardiopulmonary exercise testing. Our data indicate that SSc patients with normal resting pulmonary hemodynamics may have abnormal pulmonary hemodynamics during exercise. We therefore view this study as generating a hypothesis and as a basis for a larger placebo-controlled trial.

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. Rajeev Saggar 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.

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Analysis and interpretation of data. Rajeev Saggar, Khanna, Shapiro, Furst, Maranian, Clements, Dua, Belperio, Rajan Saggar.

ROLE OF THE STUDY SPONSOR

Gilead Sciences had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Gilead Sciences.

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