Treprostinil, a Prostacyclin Analogue, in Pulmonary Arterial Hypertension Associated With Connective Tissue Disease*

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Study objectives: To assess the efficacy and safety of continuous subcutaneous infusion of treprostinil, a stable prostacyclin analogue, for treating pulmonary arterial hypertension (PAH) in patients with connective tissue disease (CTD).

Design: Two multicenter, randomized, double-blind, placebo-controlled, prospective trials of treprostinil vs placebo in 470 patients with PAH.

Patients: A subset of 90 patients with PAH and CTD, including systemic lupus erythematosus, diffuse scleroderma, limited scleroderma, and mixed CTD/overlap syndrome.

Interventions: Patients received either treprostinil (initiated at 1.25 ng/kg/min, and titrated upward) or placebo via continuous subcutaneous infusion. The maximum dose of treprostinil allowed was 22.5 ng/kg/min.

Measurements: Six-minute walk (6MW) distance and dyspnea-fatigue scores were determined at baseline, and at 6 weeks and 12 weeks. Hemodynamic measures were obtained at baseline and at 12 weeks.

Results: At baseline, most patients had New York Heart Association class III symptoms. The mean baseline 6MW distance was 289 m (range, 60 to 448 m). The mean dose of treprostinil at week 12 was 8.4 ng/kg/min (range, 1.25 to 17.5 ng/kg/min). After 12 weeks, the change in cardiac index from baseline was + 0.2 ± 0.08 L/min/m² in the treprostinil group and − 0.07 ± 0.07 L/min/m² in the placebo group (p = 0.007). The pulmonary vascular resistance index decreased by 4 ± 2 U × m² in the treprostinil group and increased by 1 ± 1 U × m² in the placebo group (p = 0.006). The placebo-corrected median improvement from baseline in 6MW distance was 25 m in treprostinil-treated patients (p = 0.055); this improvement appeared to be dose related. Dyspnea fatigue scores also improved in the treprostinil group compared with the placebo group (p = 0.014). Adverse events included infusion site pain and typical side effects related to prostaglandins, and were tolerated by most patients.

Conclusions: Continuous subcutaneous infusion of treprostinil in patients with PAH associated with CTD improved exercise capacity, symptoms of PAH, and hemodynamics.

(CHEST 2004; 126:420–427)

Key words: connective tissue disease; hemodynamics; prostacyclin; pulmonary arterial hypertension; Remodulin; scleroderma; systemic lupus erythematosus; treprostinil

Abbreviations: CTD = connective tissue disease; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary arterial pressure; 6MW = 6-min walk; SLE = systemic lupus erythematosus

Pulmonary arterial hypertension (PAH) is a serious complication of many types of connective tissue disease (CTD).1 Once diagnosed, it is difficult to treat and has a very poor prognosis.2,3 Placebo-controlled studies, and studies comparing epoprostenol to conventional therapy have shown that epoprostenol increases exercise capacity in patients with PAH and the scleroderma spectrum of disease,4–6 and improves hemodynamics and exercise capacity in patients with systemic lupus erythematosus (SLE).7,8 IV epoprostenol is approved by the US Food and Drug Administration for the treatment of PAH associated with the scleroderma spectrum of disease. The administration of epoprostenol is complex, however, and its extremely short half-life dictates that it be administered with an infusion pump and given via continuous IV infusion via a surgically implanted central venous catheter. Because of these
issues, there are significant concerns regarding catheter-related infections, thromboembolic events, and abrupt discontinuation of the infusion, which can lead to episodes of worsening PAH and hemodynamic decompensation.\textsuperscript{9} Epoprostenol must also be mixed daily under sterile conditions, and requires that the drug be kept cold using ice packs during infusion, making it a cumbersome and inconvenient treatment option in this patient population.\textsuperscript{10}

The prostacyclin analogue treprostinil has recently been approved by the US Food and Drug Administration for the treatment of PAH in patients with New York Heart Association (NYHA) class II to IV symptoms. Treprostinil has short-term hemodynamic effects similar to epoprostenol\textsuperscript{11}; however, treprostinil has a longer half-life of 2 to 4 h when administered by subcutaneous infusion, and is stable at room temperature.\textsuperscript{12} The improved stability of this compound and its solubility at physiologic pH enables subcutaneous delivery, thereby avoiding the potential complications of the epoprostenol IV delivery system. A large, multicenter trial, designed to study the safety and efficacy of chronically administered, continuous subcutaneous infusion of treprostinil in 470 patients with idiopathic PAH, PAH associated with congenital heart disease, and PAH associated with CTD was recently completed and reported by Simonneau et al.\textsuperscript{13} We describe successful therapy of PAH with continuous subcutaneous treprostinil infusion in the subset of patients with CTD from this study.

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A list of study participants is given in the Appendix.

This work was funded by United Therapeutics Corporation, Research Triangle Park, NC.

The authors have financial relationships with United Therapeutics Corporation, the sponsor of the study. These relationships include consulting and support for work as investigators and study coordinators.

Manuscript received September 4, 2004; revision accepted February 3, 2004.

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**MATERIALS AND METHODS**

In a large, multicenter, double-blind, placebo-controlled, 12-week trial, 470 patients with PAH aged 12 to 75 years were randomized to receive a continuous, subcutaneous infusion of treprostinil or placebo, according to the following inclusion criteria (previously described\textsuperscript{\textsuperscript{13}}): NYHA functional class II, III or IV despite treatment with conventional therapy (ie, anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides, and supplemental oxygen), mean pulmonary artery pressure (PAPm) ≥ 25 mm Hg, pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mm Hg, pulmonary vascular resistance ≥ 3 Wood units, and baseline 6-min walk (6MW) distance between 50 m and 450 m. Exclusion criteria included significant parenchymal lung disease as evidenced by radiographic changes, total lung capacity < 60% predicted or FEV$_1$/FVC ratio of < 50%, chronic thromboembolic pulmonary hypertension, valvular heart disease, pericardial constriction, left ventricular dysfunction, renal dysfunction (serum creatinine > 2.5 mg/dl), pregnancy, or uncontrolled sleep apnea. Written informed consent was obtained for all patients or guardians prior to study initiation; the study protocol was approved by the institutional review board of each of the participating centers. The study design is depicted in Figure 1.

The present retrospective subgroup analysis describes results for the 90 patients in the above study with PAH associated with CTD, including SLE (n = 25), diffuse scleroderma (n = 25), limited scleroderma (n = 20), and mixed CTD/overlap syndrome (n = 20). Forty-nine patients received placebo and 41 received treprostinil. Borg dyspnea scores\textsuperscript{14} and dyspnea-fatigue ratings\textsuperscript{15} were obtained in conjunction with the 6MW test at baseline. For all patients, right-heart catheterization was performed using a flow-directed, balloon flotation catheter within 2 days of the initial 6MW test and again at the end of 12 weeks. Patients also underwent a quality-of-life assessment using an adapted version of the Minnesota Living With Heart Failure Questionnaire\textsuperscript{16} at baseline and at week 12.

After baseline evaluation, patients were randomized to receive either continuous subcutaneous treprostinil or placebo via a portable positive pressure microinfusion pump (MiniMed Model 506; MiniMed Technologies; Sylmar, CA) in addition to conventional therapy, which had been optimized for at least 1 month prior to study enrollment. Placebo or treprostinil at a dose of 1.25 to 2.5 ng/kg/min were initiated in the hospital, and doses were up-titrated in increments of 1.25 to 2.5 ng/kg/min every 1 to 2 weeks on an outpatient basis. The target dose was based on response to therapy and adverse effects, and did not exceed 22.5 ng/kg/min. Prior to initiation of study drug, patients were trained by a clinical nurse specialist to prepare the study medication, insert the subcutaneous catheter, and operate the infusion pump.

**Statistical Analysis**

Statistical analysis was performed using a Fisher exact test for categorical variables and/or Wilcoxon rank-sum test for continuous variables. Changes in the distance walked in 6 min from baseline to week 12 were compared between treatment groups using an intention-to-treat, nonparametric analysis of covariance. A least-squares regression analysis was applied to calculate the 6MW distances as linear functions of baseline walk, vasodilator use, and study center. The standardized mid-ranks of the residuals from these linear regression analyses were then determined. Patients who discontinued the study due to death prior to week 12 or were too ill to perform the week 12 walk assessment were assigned a rank of zero (ie, “worst rank”). For patients who discontinued prior to week 12 for any other reason, the standardized mid-rank from the last available assessment was carried
forward. The ranks were then compared between treatment groups using the extended Cochran-Mantel-Haenszel test. Data are presented as mean ± SE. For summary purposes, patients who discontinued the study due to death prior to week 12 or were too ill to perform the week 12 walk assessment were assigned a walk distance of 0 m. Those who discontinued prior to week 12 for any other reason had their last walk distance carried forward.

Changes from baseline to week 12 in the composite score of signs and symptoms of PAH, dyspnea-fatigue rating, Borg dyspnea score, and quality-of-life scores were compared between treatment groups using the Wilcoxon rank-sum test without imputation. Changes in hemodynamic variables were compared between treatment groups using parametric analysis of covariance adjusting for baseline value without imputation. A significance level of α = 0.05 was used to identify a treatment effect. Data are reported as mean ± SE.

Results

Ninety patients from the original 470 patients enrolled in the PAH multicenter trial were diagnosed with PAH associated with CTD. Baseline demographics and hemodynamics for patients with CTD are shown in Tables 1, 2, respectively. The baseline 6MW distance was 280 ± 13 m for the treprostinil group, and 296 ± 13 m for the placebo group (p = 0.28). There were no significant differences in baseline demographics, hemodynamics, 6MW distances, CTD diagnosis, or NYHA functional class between the placebo and treprostinil groups.

Three patients in the treprostinil group discontinued the study prior to week 12 due to adverse events; one patient died. There were three deaths in the placebo group. Of the remaining patients, the mean dose of study drug achieved at week 12 was 8.4 ± 0.7 ng/kg/min in the active treatment group and 17.8 ± 0.8 ng/kg/min in the placebo group (p < 0.001).

Treprostinil and Exercise Capacity

After 12 weeks, the 6MW distance for treprostinil-treated patients completing the study was 305 ± 16 m, a mean difference of +24 ± 12 m compared to baseline; in contrast, the distance achieved for placebo-treated patients completing the study was 303 ± 14 m, a mean difference of +3 ± 8 m compared to baseline, yielding a placebo-corrected difference of 21 m.

Table 1—Baseline Characteristics of Patients with PAH and CTD*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Treprostinil (n = 41)</th>
<th>Placebo (n = 49)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>54 ± 2</td>
<td>48 ± 2</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td>0.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (7)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38 (93)</td>
<td>43 (88)</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.28†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3 (7)</td>
<td>6 (12)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>29 (71)</td>
<td>38 (78)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>9 (22)</td>
<td>5 (10)</td>
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<tr>
<td>Diagnosis</td>
<td>0.15†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited scleroderma</td>
<td>13 (32)</td>
<td>7 (14)</td>
<td></td>
</tr>
<tr>
<td>Diffuse scleroderma</td>
<td>12 (29)</td>
<td>13 (27)</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>7 (17)</td>
<td>18 (37)</td>
<td></td>
</tr>
<tr>
<td>MCTD</td>
<td>8 (20)</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>Overlap syndromes</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Exercise capacity, 6MW</td>
<td>280 ± 13</td>
<td>296 ± 13</td>
<td>0.28</td>
</tr>
<tr>
<td>test, m</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SE or No. (%). MCTD = mixed connective tissue disease.
†p Value computed across all categories simultaneously.
In order to reduce the effect of extreme (very high or very low) values in 6MW distance, we evaluated the median changes in 6MW distance between groups. After applying imputation for patients not completing the trial, the median change for patients in the active treatment group was 10 m at week 12, compared to 0 m in the placebo group. To evaluate the difference between groups in median distance walked, the Hodges-Lehmann median effect size was used, resulting in a 25-m difference \( (p = 0.055) \).

Improved exercise capacity in the treprostinil group appeared to be the greatest in patients in the highest dose quartile \( (Fig \ 2) \), although this was not statistically significant. In addition to their increased exercise capacity, patients in the treprostinil group experienced an improvement in dyspnea-fatigue rating \( (p = 0.014) \) \[Table 2\].

There was no difference in Borg dyspnea score between the treprostinil and placebo groups \( (\pm 0.6 \pm 0.5, \text{ and } \pm 0.2 \pm 0.5, \text{ respectively;} \quad p = 0.168) \). How-
ever, to determine the effect of treprostinil on the combined measures of Borg dyspnea score and 6MW distance ("Borg walk effect"), we plotted cumulative frequency distribution curves that combined the ranks of the change in 6MW distance with the ranks of the change in Borg dyspnea score for individual patients at the end of week 12 (Fig 3). Patients who had an improvement in both distance and symptoms were assigned the highest rank, those with an improvement in one but deterioration in the other were assigned middle ranks, and those with deterioration in both were assigned the lowest rank. Using this approach, treprostinil-treated patients experienced an improvement in 6MW distance, Borg dyspnea score, or both, compared to placebo (p = 0.02).

**Treprostinil and Hemodynamics**

Treprostinil-treated patients showed a trend toward improvements from baseline in PAPm (p = 0.095), and mean right atrial pressure (p = 0.056), and significant, albeit modest improvements in cardiac index (p = 0.007) and pulmonary vascular resistance index (p = 0.006) compared with patients receiving placebo (Table 2). There were no statistically significant differ-
ences in pretreatment and posttreatment hemodynamic variables between patients with different CTDs.

**Quality of Life**

Patients receiving treprostinil experienced a trend toward improvement over the 12 weeks of treatment in the physical dimension score of the Minnesota Living with Heart Failure Questionnaire compared with patients in the placebo group (−5.6 ± 1.8 vs −1.1 ± 1.5, respectively; p = 0.075).

**Tolerability and Safety**

Dose-limiting adverse events in the treprostinil group included infusion site pain and local reactions, diarrhea, headache, nausea, jaw pain, chest pain, backache, and restlessness. Infusion site pain was more frequent in the treprostinil group (83% vs 22% compared with placebo); however, most patients tolerated the treprostinil infusion. Of the 90 patients with CTD enrolled in the multicenter trial, 7 patients discontinued therapy prematurely: 3 treprostinil-treated patients reported intolerable adverse effects (related to site pain), and 4 patients (1 in the treprostinil group and 3 in the placebo group) died (p = not significant). The frequency of occurrence of serious adverse events was similar in both groups, and none were attributed to study drug.

**Discussion**

In the subset of patients with PAH associated with CTD from the large PAH multicenter trial studying treprostinil vs placebo, continuous subcutaneous infusion of treprostinil improved exercise capacity, hemodynamics, dyspnea-fatigue rating, and physical aspects of quality of life compared with placebo. Adverse events with treprostinil were similar to those observed in clinical trials of epoprostenol, with the exception of infusion site pain, which was seen in the majority of treprostinil-treated patients, but did not result in greater discontinuation rates compared with placebo. Infusion site pain improved over several months.

After 12 weeks, patients receiving treprostinil walked a mean of 21 m further in the 6MW test compared with patients receiving placebo. In order to adhere to our intention-to-treat principle for the primary analysis, all patients randomized in this subgroup of CTD patients were included in a rank-based analysis. We chose this strategy because rank-based approaches are not overly influenced by deaths the way ordinary parametric approaches (such as t tests or analysis of variance) would be. Thus, patients who died were assigned a distance of 0 m for purposes of numeric summaries, and only medians and the Hodges-Lehmann median treatment difference (rank-based statistics) were presented, which should not be disproportionately influenced by the 0-m assignments the way means would be. Using an alternative approach, when an analysis was performed excluding from the analysis subjects who died, the placebo-corrected median improvement from baseline in 6MW distance was 19 m for the treatment group (p = 0.08).

The relatively moderate increase in 6MW distance after 3 months of continuous subcutaneous treprostinil in this study may be due in part to the low dose of treprostinil (≤ 9 ng/kg/min) achieved in 26 of the 37 patients who completed the trial (Fig 2). Target doses of treprostinil after 12 weeks of therapy were not reached because of the assumption by the study participants that infusion site pain was dose related, limiting their up-titration of study drug.

The current study showed that patients receiving the highest dose of treprostinil tended to show the greatest improvement in distance walked in 6 min (Fig 2), similar to that seen for the patients in the main study. Thus, had more patients reached their target dose in these studies, it is possible that the mean improvement in 6MW distance with treprostinil may have been greater. As the 6MW test is considered an independent predictor of mortality in idiopathic PAH, any significant improvement in this measurement due to treatment may reflect important clinical gains.

Increases in exercise capacity in the CTD subset of patients in this study are also reflected by the significant improvements in dyspnea-fatigue ratings observed in the patients receiving treprostinil, and by the change in dyspnea-fatigue ratings when analyzed in combination with the change in 6MW distance (Fig 3). While the significance of this Borg walk analysis is as yet unproven, it may reflect a quality-of-life parameter worthy of validation in future studies. Thus, until such studies are performed, caution must be used in interpreting such an analysis.

Several unique properties of treprostinil simplify the daily routine associated with prostacyclin therapy in patients with PAH. The biological half-life of treprostinil administered by continuous subcutaneous infusion is 2 to 4 h, which is significantly longer than the half-life of epoprostenol. This may decrease the potential for adverse events associated with inadvertent, abrupt discontinuation of the drug, such as an acute worsening of PAH symptoms. In addition, in contrast to epoprostenol, treprostinil is chemically stable at physiologic pH, a property that allows for administration by subcutaneous infusion, thereby eliminating the need for surgical placement of a central venous catheter with its attendant risks.
Treprostinil is also stable at room temperature, and thus requires neither continuous refrigeration nor daily mixing. Finally, a smaller infusion pump is used for treprostinil infusion compared to epoprostenol.

In summary, analysis of data from the subset of patients with PAH associated with CTD from the large multicenter trial showed that treprostinil stabilized and/or improved clinical measures of PAH severity in this high-risk patient population. Treprostinil was well tolerated, with infusion site discomfort being the most commonly reported adverse event. Study participants were cautious in their upward titration of study drug due to a belief that drug-related site pain was dose related. However, because the salutary effects of treprostinil were dose related, the magnitudes of the improvements seen may have underestimated the true clinical benefits of treprostinil. Further study involving long-term treatment with treprostinil is warranted to determine whether these clinical benefits are sustained or may be further improved with longer duration and higher dose escalation.

Limitations

This original multicenter trial was not designed to prospectively study subgroups of PAH patients. Furthermore, the trial studied the effects of treprostinil after only 12 weeks of treatment. While this time interval has been commonly used in previous multicenter trials of PAH therapies, other studies have suggested that an interval of 12 weeks may not accurately reflect longer-term responses. This is of particular concern, since patients with PAH and underlying CTD have higher mortality rates than patients with other forms of PAH. Thus, the results of this retrospective analysis of PAH patients with CTD must be interpreted with caution. Finally, while the response to treprostinil appears to be dose-related, the prevalence of infusion site pain may be significant enough to preclude timely up-titration in some patients, thereby limiting the overall clinical benefit of the drug.

APPENDIX

The Treprostinil Study Group: Alejandro Arroliga, MD, The Cleveland Clinic; David Badesch, MD, University of Colorado Health Sciences Center; Issahar Ben-Dov, MD, The Chaim Sheba Medical Center, Israel; Robert Bourge, MD, University of Alabama Medical Center; Carol Black, MD, Royal Free Hospital, United Kingdom; Paul Corris, MD, Freeman Hospital, United Kingdom; Ben deBoisblanc, MD, Louisiana State University Medical Center; Teresa DeMarco, MD, University of California San Francisco; Ramona Doyle, MD, Stanford University Medical Center; Jeffrey Edelman, MD, Oregon Health Sciences University; Greg Elliott, MD, LDS Hospital; Adaani Frost, MD, Baylor College of Medicine; John Granot, MD, Toronto General Hospital; Nicholas Hill, MD, Tufts-New England Medical Center; Anne Keogh, MD, St. Vincent’s Hospital, Sydney, Australia; David Kiely, MD, Royal Hallamshire Hospital, United Kingdom; Mordechai Kramer, MD, Rabin Medical Center, Israel; David Langleben, MD, and Andrew Hirsch, MD, Jewish General Hospital, Montreal, Clint Lawrence, MD, Emory School of Medicine; Michael McGoon, MD, Mayo Clinic; Srinivas Murari, MD, University of Pittsburgh Medical Center; Robert Naeije, MD, ULB Hospital Erasme, Belgium; David Ostrow, MD, Vancouver General Hospital; Andrew Peacock, MD, The Scottish Pulmonary Vascular Unit. United Kingdom; Ivan Robbins, MD, Vanderbilt University Medical Center; David Ross, MD, UCLA School of Medicine; Melvyn Rubenfire, MD, University of Michigan; Miguel Gomez-Sanchez, MD, Hospital 12 de Octubre, Madrid; Shelley Shapiro, MD, PhD, University of Southern California; Victor Tapson, MD, Duke University Medical Center; Adam Torbicki, MD, National Tuberculosis and Lung Disease Research, Poland; Aaron Waxman, MD, PhD, Tufts-New England Medical Center; Joel Wirth, MD, Chest Medicine Associates; Diane Zwieck, MD, St. Lukes Medical Center.

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REFERENCES

7 Robbins IM, Gaine SP, Schilz R, et al. Epoprostenol for...
8 Mok MY, Tse HF, Lau CS. Pulmonary hypertension secondary to systemic lupus erythematosus: prolonged survival following treatment with intermittent low dose iloprost. Lupus 1999; 8:326–331