RITZ-5: Randomized Intravenous TeZosentan (an Endothelin-A/B Antagonist) for the Treatment of Pulmonary Edema

A Prospective, Multicenter, Double-Blind, Placebo-Controlled Study

Edo Kaluski, MD, FACC,* Isaac Kobrin, MD,|| Reuven Zimlichman, MD,† Alon Marmor, MD,‡ Oscar Krakov, MD,§ Olga Milo, MD,* Aline Frey, PhARMD,|| Shoshana Kaplan, MD,* Rikardo Krakover, MD,* Avi Caspi, MD,|| Zvi Vered, MD, FACC,* Gad Cotter, MD,* for the RITZ-5 Investigators

Zerifin, Holon, Safad, and Rehovot, Israel; and Allschwil, Switzerland

OBJECTIVES

The objective of this study was to evaluate the addition of intravenous (IV) tezosentan to standard therapy for patients with pulmonary edema.

BACKGROUND

Tezosentan is an IV nonselective endothelin (ET)-1 antagonist that yields favorable hemodynamic effects in patients with acute congestive heart failure (CHF).

METHODS

Pulmonary edema was defined as acute CHF leading to respiratory failure, as evidenced by an oxygen saturation (SO₂) <90% by pulse oximeter despite oxygen treatment. All patients received oxygen 8 l/min through a face mask, 3 mg of IV morphine, 80 mg of furosemide, and 1 to 3 mg/h continuous drip isosorbide-dinitrate according to their blood pressure level and were randomized to receive a placebo or tezosentan (50 or 100 mg/h) for up to 24 h.

RESULTS

Eighty-four patients were randomized. The primary end point, the change in SO₂ from baseline to 1 h, was 9.1 ± 6.3% in the placebo arm versus 7.6 ± 10% in the tezosentan group (p = NS). The incidence of death, recurrent pulmonary edema, mechanical ventilation, and myocardial infarction during the first 24 h of treatment was 19% in both groups. Reduced baseline SO₂, lower echocardiographic ejection fraction, high baseline mean arterial blood pressure (MAP), and inappropriate vasodilation (MAP reduction at 30 min of <5% or >30%) correlated with worse outcomes. A post-hoc analysis revealed that the outcome of patients who received only 50 mg/h tezosentan was better than patients in the placebo group whereas patients receiving 100 mg/h had the worst outcomes.

CONCLUSIONS

In the present study, tezosentan (an ET-1 antagonist) did not affect the outcome of pulmonary edema, possibly because of the high dose used. (J Am Coll Cardiol 2003;41: 204–10) © 2003 by the American College of Cardiology Foundation

In previous studies (1–4) it was demonstrated that acute cardiogenic pulmonary edema results from a rapidly deteriorating cycle of events in which patients with reduced baseline systolic and diastolic reserve are faced with an acute increase in systemic vascular resistance and, hence, afterload. This causes an acute compensated state, leading to decreased peripheral perfusion, neurohormonal activation, decreasing left ventricular function, and increasing vascular resistance. The result of this vicious cycle is an increase in left ventricular end-diastolic pressure that is transmitted backwards to the pulmonary vasculature, causing an acute increase in pulmonary capillary pressure and the transudation of fluid from the intravascular compartment to the lung interstitium and alveoli, leading in turn to the full-blown syndrome of acute cardiogenic pulmonary edema.

Endothelin (ET)-1 is one of the most potent and long-lasting endogenous vasoconstrictors isolated to date (5). It is elevated in certain clinical situations, including congestive heart failure (CHF) (6). Endothelin-1 (7) and big ET (8) are markedly elevated in chronic CHF (9), and serum levels correlate with prognosis. Tezosentan is an intravenous (IV) nonselective ET-1 blocker. In two separate phase II studies in patients with severe chronic CHF (10,11) and in one phase III study in patients with acute CHF (G. Torre-Amione et al., unpublished data, 2002), it was demonstrated that maximal hemodynamic effects of tezosentan in patients with chronic heart failure can be accomplished with doses of 25 to 50 mg/h. These beneficial effects yielded improved cardiac index and reduced systemic and pulmonary vascular resistance, as well as pulmonary capillary wedge pressure.

Therefore, the main assumption of the Randomized Intravenous TeZosentan (RITZ)-5 study was that because ET-1 is a potent vasoconstrictor occurring in high levels in patients with CHF, by rapidly blocking its action with the receptor antagonist tezosentan, significant vasodilation will occur, which then will improve the condition of patients more rapidly (that is, a faster improvement in oxygen saturation [SO₂]) and decrease the rate of refractory pulmonary edema.
ABBREVIATIONS AND ACRONYMS
- CHF = congestive heart failure
- EF = ejection fraction
- ET = endothelin
- IV = intravenous
- MAP = mean arterial blood pressure
- MI = myocardial infarction
- RITZ = Randomized Intravenous TeZosentan
- SO_{2} = oxygen saturation

PATIENTS AND METHODS

Study design. A prospective, double-blind, placebo-controlled, multicenter, parallel (1:1), phase III study to assess the efficacy and safety of IV tezosentan in addition to standard therapy in patients with acute pulmonary edema was conducted.

Inclusion criteria. Men or nonpregnant women (age >18 years) with severe acute pulmonary edema defined as acute CHF exacerbation accompanied by an SO_{2} <90% while receiving oxygen 8 l/min who were able and willing to sign an informed consent were included in the study. A chest X-ray was not used for inclusion because it is not available on mobile intensive care units, which is where most patients were recruited.

Exclusion criteria. Exclusion criteria for patients were as follows: systolic blood pressure <110 mm Hg; hemodynamically significant arrhythmias; acute coronary syndrome with ST-segment elevation; active myocarditis; hypertrophic obstructive cardiomyopathy; stenotic valvular disease; restrictive or constrictive pathology; congenital heart disease; or pericarditis. Also excluded were patients with: noncardiac pulmonary edema; clinical evidence of digoxin toxicity; hemodynamic supporting devices; acute or chronic dialysis; systemic illnesses; sepsis; terminal illness; or previous exposure to tezosentan.

Study medication. Intravenous tezosentan (Actelion Ltd., Allschwil, Switzerland) 50 mg/h for 15 to 30 min followed by IV isosorbide dinitrate drip (1 to 3 mg/h), and IV morphine sulfate (3 mg bolus). Randomized patients received either IV tezosentan or placebo. Patients were followed up for 30 days after enrollment.

Concomitant medications. Parenteral inotropes, sympathomimetics, or vasodilators initiated at least 2 h before randomization could continue to be used during the study. However, the dose had to be kept constant for at least 6 h after the initiation of the study medication. Increasing the doses of these medications was reserved for those with worsening CHF or an inadequate response to the protocol.

Primary end point. The primary end point was defined as the change from baseline to 60 min in arterial SO_{2} as measured by pulse oxymetry.

Secondary end points. The secondary end points were as follows:
1. death, mechanical ventilation, recurrent pulmonary edema, or new myocardial infarction (MI) during first 24 h of treatment;
2. a change in SO_{2} from baseline to 15, 30, 45, 60, 75, 90, 120, 240, or 360 min;
3. all cause mortality and rehospitalizations within 30 days of treatment initiation;
4. evidence of acute MI in the first 24 h of treatment, and
5. initiation or increase in treatment of IV inotropic, sympathomimetic, or vasodilator therapy for heart failure during the first 24 h.

Predictors of outcome. Although measures of treatment success in pulmonary edema are not generally available, we have suggested, based on previous studies (1–4), some criteria for treatment success—an increase in SO_{2}, specifically to above 95%—and treatment failure—the occurrence of refractory pulmonary edema, that is, pulmonary edema not improving despite the abovementioned treatment, instead requiring further aggressive vasodilator treatment or mechanical ventilation and acute MI during the first 24 h of treatment. Based on those studies, important predictors of treatment success or failure included: baseline SO_{2} (as a measure of disease severity); echocardiographic resting ejection fraction (EF) as a measure of lower left ventricular contractility reserve; and higher baseline mean arterial blood pressure (MAP) as a measure of higher baseline systemic vascular resistance. We also analyzed whether appropriate vasodilation (defined as a decrease of 5% to 30% in MAP at 30 min since treatment initiation [12]) as a measure of appropriate therapeutic response to vasodilators was a predictor of treatment success or failure.

Statistical analysis. The planned sample size of 50 patients randomized equally to tezosentan or placebo was calculated to detect with 90% power a difference between treatments of 6% (standard deviation = 6%) on the mean change from baseline to 1 h in SO_{2} at a two-sided alpha level of 0.05 using the Student t test. The sample size estimation in this situation depends exclusively on the effect size, which is 1.0.

Subsequently, a new requirement was determined to have sufficient power to detect a difference in an exploratory analysis of the incidence of the combined end point of death, mechanical ventilation, recurrent pulmonary edema, or new MI during the first 24 h of randomized therapy. To detect a clinically relevant reduction in event rates from 50% in the placebo arm to 15% in the tezosentan arm by means of the Fisher exact test, the sample size was increased to 84 patients (42 patients per treatment arm). As a result of this increase in sample size, the power of the hypothesized test on the primary end point increased from 90% to >99%. Alternatively, with a sample size of 42 patients per group, a two-sided alpha level of 0.05, and the common standard deviation of 6%, the study has 90% power to detect a
difference of 4.3% in the primary end point as statistically significant.

Location and scale statistics were calculated and displayed for the numeric parameters (mean, standard deviation, standard error of the mean, 95% confidence interval of the mean, median, first, and third quartiles, minimum and maximum). Exploratory p values for comparisons were from the Student t test.

Proportions and 95% confidence intervals were computed for the incidences. Exploratory p values for comparisons were from the Fisher exact test.

Kaplan-Meier estimates were computed for the proportions of event-free patients for the different events defined in the protocol. Exploratory p values for comparisons were from the log-rank test.

Statistical analyses were based on the intention-to-treat population. All p values were two-sided, with a value of p < 0.05 considered significant.

RESULTS

Baseline characteristics. As seen in Table 1, the two study arms were similar and well balanced.

Study end points. At 60 min, the improvement in arterial SO2 was similar in the tezosentan and placebo arms (7.6 ± 10.0 vs. 9.1 ± 6.3, p = 0.29). The rest of the end points assessed were not different between the two arms. In the 30-day analysis, there were also no significant differences between the tezosentan and placebo arms. Regarding safety, hypotension was more common in the tezosentan arm (19% vs. 38%, p = 0.05), although this did not occur during the first hour of treatment, when the patients were in the acute phase of pulmonary edema, but rather during the maintenance phase. Also, although no statistically significant difference in the rate of renal failure was observed when comparing the two treatment arms, there was a statistically significant larger mean rise in serum creatinine in the tezosentan arm (3 ± 17 μmol/l vs. 19 ± 29 μmol/l, p = 0.024) (Table 2). Concomitant medications administered during the study period are presented in Table 3.

Predictors of outcome in patients with acute pulmonary edema. In analyzing the results of our study we found that lower baseline SO2, higher baseline MAP, and lower baseline echocardiographic EF were predictors of limited treatment success as measured by lower 1-h SO2 and increased rate of refractory pulmonary edema or MI at 24 h follow-up whereas appropriate vasodilation was a predictor of improved treatment success (Tables 4 to 6). We have also performed an analysis of these predictors in patients in the placebo group only, and the effect of these predictors was virtually identical. Hence, the results of the whole group are presented.

Post-hoc analysis of the effect of tezosentan. Because we did not observe any significant effect of tezosentan after the planned analysis of the study, we performed two post-hoc analyses of the data.

First, we compared the time-course of blood pressure decrease in the tezosentan and placebo arms both during the first hour as well as during 24 h of treatment (Figs. 1A and 1B). This analysis showed that adding tezosentan to standard treatment for acute cardiogenic pulmonary edema did not lead to further decrease in blood pressure during the first hour of treatment (Fig. 1A). However, thereafter, tezosentan induced a significant decrease in blood pressure lasting up to 6 h (Fig. 1B), necessitating down-titration of the tezosentan dose in many patients.

Second, we analyzed separately the time-to-death or recurrent pulmonary edema in patients who received placebo versus those receiving tezosentan. Furthermore, the time-course in patients who received tezosentan 50 mg/h versus those receiving 100 mg/h was analyzed separately (Fig. 2), although this was not a prespecified analysis and patients had not been randomized to one of the two doses. These two doses had at that time been studied in the randomized, parallel-group, placebo-controlled RITZ-2
study (G. Torre-Amione et al., unpublished data, 2002), hence, the use of either dose was arbitrarily decided by the first treating physician. In this analysis we found that the use of tezosentan 100 mg/h was related to more adverse events during follow-up as compared with placebo, whereas patients treated by tezosentan 50 mg/h fared better than placebo-treated patients.

DISCUSSION

Acute cardiogenic pulmonary edema is a common life-threatening syndrome. However, its pathogenesis has seldom been explored and no prospective, placebo-controlled studies have been performed regarding its treatment. We have recently proposed a novel approach to this syndrome (3,13). Our main hypothesis was that pulmonary edema is related to significant peripheral vasoconstriction induced by inflammatory and neurohormonal activation. This in turn imposes a severe afterload mismatch on the already jeopardized left ventricle, causing a further deterioration of its function and leading to an increase in left ventricular end-diastolic pressure. The increased pressure is transmitted backwards to the pulmonary veins and capillaries, causing fluid transudation to the lung parenchyma and alveoli, impairing blood oxygenation and, therefore, reducing systemic saturation. The end result is a progressive syndrome of respiratory and circulatory failure that, if remaining untreated, will cause rapid deterioration and death.

As previously stated, ET is a strong vasoconstrictor. Its levels are significantly increased in patients with acute CHF, and tezosentan is a potent ET antagonist administered intravenously that was developed specifically for the treatment of acute heart failure. Based on our hypothesis that pulmonary edema is related to significant peripheral vasoconstriction (1–4) and our previous experience showing that vasodilators are effective in the treatment of this syndrome

Table 3. Most Frequent Concomitant Medications

<table>
<thead>
<tr>
<th>Medication N (%)</th>
<th>Placebo (n = 42)</th>
<th>Tezosentan (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>25 (59.5)</td>
<td>19 (45.2)</td>
</tr>
<tr>
<td>Statins</td>
<td>26 (61.9)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Antiarrhythmics, class I and III</td>
<td>14 (33.3)</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>18 (42.9)</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>9 (21.4)</td>
<td>11 (26.2)</td>
</tr>
<tr>
<td>Adrenergic and dopaminergic agents</td>
<td>3 (7.1)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12 (28.6)</td>
<td>6 (14.3)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>36 (85.7)</td>
<td>35 (83.3)</td>
</tr>
</tbody>
</table>

Table 4. Predictors of Improvement in 60 min \( SO_2 \) to >95%

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory pulmonary edema</td>
<td>0</td>
<td>15%</td>
<td>0.016</td>
</tr>
<tr>
<td>Acute MI (%)</td>
<td>3</td>
<td>21</td>
<td>0.014</td>
</tr>
<tr>
<td>Echocardiographic EF (%)</td>
<td>44 ± 12</td>
<td>35 ± 11</td>
<td>0.05</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>125 ± 16</td>
<td>115 ± 27</td>
<td>0.09</td>
</tr>
<tr>
<td>Baseline</td>
<td>100 ± 16</td>
<td>101 ± 19</td>
<td>0.74</td>
</tr>
<tr>
<td>MAP decrease at 30 min (%)</td>
<td>12.5 ± 12</td>
<td>5.5 ± 13.5</td>
<td>0.015</td>
</tr>
<tr>
<td>Appropriate vasodilatation (%)</td>
<td>62</td>
<td>40</td>
<td>0.05</td>
</tr>
</tbody>
</table>

EF = ejection fraction; MAP = mean arterial blood pressure; MI = myocardial infarction; \( SO_2 \) = oxygen saturation.
Lower baseline echocardiographic EF, which was a strong predictor of both 1-h SO₂ as well as refractory pulmonary edema. However, the results of this study demonstrate that the administration of IV tezosentan at the current dose and dosing schedule did not more effectively treat pulmonary edema and could lead to side effects, such as hypotension or renal dysfunction. A few mechanisms, stated in the following paragraphs, could explain why an apparently effective vasodilator did not affect the outcome of these patients.

The role of ET-1 in acute pulmonary edema. Although there is evidence that ET-1 levels are increased in chronic heart failure and are associated with worsening symptoms and adverse prognosis, the role of ET-1 in acute pulmonary edema has not yet been established. However, because increased systemic vascular resistance superimposed on reduced systolic and diastolic functional reserves is the key feature of pulmonary edema, ET-1 becomes a possible suspect. Therefore, it is mandatory in further studies to document the role of ET-1 in this syndrome.

Table 5. Predictors of Refractory Pulmonary Edema

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Yes</th>
<th>No</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8/84 (10)</td>
<td>76/84 (90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Echocardiographic EF (%)</td>
<td>33 ± 6</td>
<td>42 ± 13</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline SO₂ (%)</td>
<td>80 ± 14</td>
<td>87 ± 15</td>
<td>0.001</td>
</tr>
<tr>
<td>SO₂ at 1 h (%)</td>
<td>83 ± 9</td>
<td>94 ± 4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SO₂ increase at 1 h (%)</td>
<td>2.7 ± 10</td>
<td>7 ± 5</td>
<td>0.05</td>
</tr>
<tr>
<td>Baseline MAP (mm Hg)</td>
<td>156 ± 27</td>
<td>116 ± 24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAP at 1 h (mm Hg)</td>
<td>113 ± 31</td>
<td>99 ± 15</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline pulse</td>
<td>113 ± 23</td>
<td>95 ± 24</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline Respiration rate</td>
<td>35 ± 8</td>
<td>30 ± 8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

EF = ejection fraction, MAP = mean arterial blood pressure; SO₂ = oxygen saturation.

1. Lower baseline SO₂ was related to increased rate of refractory pulmonary edema. Furthermore, slower improvement in SO₂ was related to increased incidence of MI during the first 24 h. This emphasizes the pivotal role of systemic oxygen desaturation in the final deterioration of patients with pulmonary edema not only in determining the respiratory failure but also leading to further circulatory failure caused by myocardial ischemia.

2. Lower baseline echocardiographic EF, which was a strong predictor of both 1-h SO₂ as well as refractory pulmonary edema.

3. Higher baseline MAP, which was a strong predictor of both refractory pulmonary edema as well as lower 1-h SO₂.

As previously stated, our hypothesis regarding the pathogenesis of pulmonary edema involves a critical interaction between left ventricular contractile reserve and systemic vascular resistance. The finding that lower echocardiographic EF and higher MAP are both predictors of adverse outcome in patients with pulmonary edema contributes to this hypothesis (because high MAP in the presence of low EF probably indicates high peripheral vascular resistance).

4. Appropriate vasodilation. In accordance with our hypothesis, we found a significant correlation between appropriate MAP decrease at 30 min (above 5% but below 30%) and 1-h SO₂ and the presence of refractory pulmonary edema. Because this was not a predefined study goal, it is difficult to comment on whether this was related to a better treatment effect or a milder disease process that was easier to control. However, this finding is in line with our previous experience regarding the relationship between appropriate vasodilation and treatment effect (12).

However, the role of ET-1 in acute pulmonary edema. Although similar doses used in previous studies for acute heart failure resulted in a favorable hemodynamic response, it is possible that the very same dose may be inappropriate for acute pulmonary edema. The study medication did decrease MAP (or systemic vascular resistance) beyond the values obtained by conventional therapy in the placebo arm. However, as Figures 1A and 1B clearly demonstrate, these effects were obtained too late. Because rapid appropriate vasodilation is essential to treatment success in acute cardiogenic pulmonary edema, this late onset of effect might explain the lack of early favorable effect of tezosentan in the present study. However, when the desirable effects were finally obtained (at 75 to 360 min), they resulted in a more pronounced decrease in MAP, which can potentially account for the increased incidence of hypotension and creatinine increase that was observed in the tezosentan group. Therefore, better definition of the appropriate (perhaps lower) dose of tezosentan is essential for further investigation of this agent in acute cardiogenic pulmonary edema.
Lack of hemodynamic monitoring. As previously stated, the therapeutic ratio of most vasodilators is rather narrow. In recent years two major studies were performed using vasodilators for the treatment of acute heart failure. These studies examined the effect of tezosentan (RITZ-1 and -2) (G. Torre-Amione et al., unpublished data, 2002) (14) and nitrates versus nesiritide (15). In both studies a beneficial effect of vasodilator treatment was more pronounced in patients who were monitored by Swan-Ganz catheters. Such monitoring was not feasible in the RITZ-5 study. It is possible that such monitoring or better definition of therapeutic goals and exclusion and inclusion criteria would have enhanced the efficacy of tezosentan and led to a more pronounced beneficial effect.

Adverse reactions. The safety profile of the dose of tezosentan used in the RITZ-5 study is consistent with the findings of the RITZ-1, -2, and -4 studies that were performed in patients with acute decompensated heart failure associated with (RITZ-4) or without (RITZ-1 and -2) acute coronary syndrome. In particularly, the RITZ-2 study in which two doses (50 and 100 mg/h) of tezosentan were compared with placebo clearly indicated that the incidence of hypotension and renal dysfunction were dose related (G. Torre-Amione et al., unpublished data, 2002).
The mechanism of renal dysfunction is unknown but could be related to an excessive vasodilatory effect on the efferent and/or the afferent arterioles of the renal glomeruli, which is similar to observations made with angiotensin-converting enzyme inhibitors (16). Interestingly, in an experimental rat model of heart failure, the acute administration of tezosentan reduced the associated renal vascular resistance and increased glomerular filtration, suggesting that if used appropriately, ET blockade might improve renal function in patients with CHF (17). During the 30-day follow-up, two and five patients died in the placebo and tezosentan groups, respectively. Three patients died one (placebo), two, and three (both on tezosentan) days after stopping treatment from cardiogenic shock, and the others died more than a week after stopping treatment from renal failure, septic shock, pulmonary edema, or sudden death. None of the deaths was assessed by the investigators as drug related. However, this trial was too small to assess any effect on mortality.

**Excessive vasodilatation.** Dual ET antagonists, such as bosentan, were shown to be effective in the treatment of severe pulmonary arterial hypertension (18). It was speculated that reduction in pulmonary pressures without improvement of cardiac function in the presence of left ventricular failure could be the reason for this observation. However, this was not seen in patients with CHF treated chronically with bosentan in the ENdothelin Antagonist Bosentan for Lowering cardiac Events in heart failure (ENABLE) study (19). In this trial, increased incidence of hospitalization for heart failure during the early phase of the trial was related to fluid retention with no evidence for increased incidence of pulmonary edema. Also in the RITZ-2 study (G. Torre-Amione et al., unpublished data, 2002) in which hemodynamic monitoring was performed in patients with acute CHF receiving the same doses of tezosentan as in the present study, excessive pulmonary vasodilation was not observed. Hence, we believe that excessive pulmonary vasodilation was not the primary reason for the lack of effect of tezosentan in the present study.

**Conclusions.** The RITZ-5 is the first prospective, randomized, placebo-controlled study exploring a new treatment for acute pulmonary edema. The study failed to show an improvement of SO₂ after 1 h of tezosentan infusion. An ad-hoc analysis indicated that the outcome of pulmonary edema is related to baseline SO₂, echocardiographic EF and MAP as well as to the MAP decrease after 30 min of treatment. Although at the present high doses and treatment regimen, tezosentan was not found effective in the treatment of acute pulmonary edema, further studies need to assess the role of ET-1 in acute pulmonary edema and to re-evaluate carefully the dose-response curves of tezosentan in this syndrome.

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