Tezosentan and Right Ventricular Failure in Patients with Pulmonary Hypertension Undergoing Cardiac Surgery: The TACTICS Trial

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Objective: **To evaluate the efficacy of tezosentan in reducing the incidence of right ventricular (RV) failure and associated mortality in patients with pre-existing pulmonary hypertension. The primary endpoint was the proportion of patients with RV failure during weaning from cardiopulmonary bypass (CPB), assessed 30 min after the end of CPB.**

Design: **Multicenter, double-blind, randomized, placebo-controlled trial.**

Setting: **Thirty-one cardiac surgical centers in 14 countries.**

Participants: **Two hundred seventy-four patients with pulmonary hypertension aged ≥18 years scheduled to undergo cardiac surgery.**

Intervention: **Intravenous tezosentan (5 mg/h) during surgery and up to 24 hours afterwards (1 mg/h), or matched placebo.**

Measurements and Main Results: **One-hundred and thirty-three patients received tezosentan and 141 placebo. RV failure occurred in 30 patients (10.9%), 37% of whom died. There was no difference in the incidence of RV failure between the two treatment groups (relative risk reduction: 0.07 [95% CI −0.83, 0.53; $p = 0.8278$]).**

Conclusion: **A reduction in RV failure with tezosentan was not observed in this study.**

(Current Controlled Trials, identifier NCT00458276).

KEY WORDS: tezosentan, endothelin receptor antagonist, pulmonary hypertension, left-sided heart disease, cardiopulmonary bypass, right ventricular failure

CARDIOPULMONARY BYPASS (CPB) requires prolonged contact between blood and artificial surfaces and is known to activate a range of mediators, including the complement cascade, thrombin, oxygen free radicals, and vasoactive molecules.[1] Consequently, CPB is associated with functional alteration of endothelial cells, which play a major role in the development of CPB-associated pulmonary hypertension (PH).[2] Patients undergoing cardiac surgery requiring CPB who develop PH during surgery are at risk of right ventricular (RV) failure. Mortality rates in these patients reportedly range from 44%−86%.[3–5]

There is currently no approved pharmacologic treatment for PH during difficult separation from CPB. In a number of animal studies, treatment with an endothelin receptor antagonist (ERA) has been shown to decrease PH, improve RV function, decrease the incidence of post-CPB pulmonary hypertensive crises and improve pulmonary compliance and oxygenation.[6] Tezosentan is a highly specific and potent competitive ERA with affinity for both the ET_A and ET_B receptor subtypes.[7] In previous phase II studies, tezosentan was shown to increased the cardiac index, decreased the systemic and pulmonary pressures, and decreased the systemic and pulmonary resistances.[8,9] Most of the effect of each dose level was achieved within 1 hour. Four double-blind, placebo controlled trials (the RITZ trials) including 1230 patients in acute heart failure have been performed.[10] Despite improvement in central hemodynamics like those described previously, these trials were unable to demonstrate a significant improvement in clinical end-point. Tezosentan has however not been used or studied in cardiac surgery where the endothelin system is activated during CPB. Increased levels of endothelin (ET-1) are associated with PH and systemic vasoconstriction, resulting in increased pulmonary vascular resistance and reduced myocardial contractility.[11–13] ET-1 levels have been shown to correlate with the duration of CPB and postoperative complications.[12,13] Increased levels of ET-1 observed during and after cardiac surgery in patients on CPB[14] also may contribute to ischemia-reperfusion injury and systemic inflammatory response, thus

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altering pulmonary endothelial function and leading to PH and RV failure. Consequently, the primary objective of the current study, Tezosentan Administration before Cardiopulmonary Bypass to Improve Cardiopulmonary Separation from Bypass (TACTICS) was to demonstrate that in patients with significant PH undergoing cardiac surgery with CPB, tezosentan through a reduction in the severity pf PH might alter the incidence of RV failure during weaning from CPB.

METHODS

Study Design

The TACTICS trial was conducted in accordance with the Declaration of Helsinki and its amendments, the International Conference on Harmonization and Good Clinical Practice guidelines, and was approved by appropriate Ethics Committees/Institutional Review Boards. Signed informed consent was obtained from all patients.

This was a prospective, multicenter, randomized, double-blind, placebo-controlled, phase III, parallel-group study and consisted of a $<$28-day screening phase, a 24-h treatment period (with potential for up to 72 h of treatment), variable duration of post-surgery hospital care, and a 28-day safety follow-up period (Fig 1).

Patients

Patients aged $\geq$18 years were eligible for inclusion into the study if they were scheduled to undergo either (1) complex cardiac surgery (defined as surgery on 2 valves, surgery on 1 valve plus revascularization or reoperation of previous valve surgery) on CPB and had preoperative PH due to left heart disease with a systolic pulmonary arterial pressure $>$40 mmHg or mean pulmonary arterial pressure $>$30 mmHg (measured by RV catheterization or echocardiography at screening) or (2) non-complex cardiac surgery on CPB and PH defined as systolic pulmonary artery pressure $>$60 mmHg.

Female patients of childbearing potential were required to use a reliable method of contraception. Patients were excluded if they had a resting systolic blood pressure $<$100 mmHg, had severe chronic obstructive pulmonary disease that might interfere with interpretation of the study results, required emergency surgery, were pregnant or breast-feeding, had used another investigational drug within 28 days before randomization, had complex adult congenital heart disease, had severe concomitant illness limiting life expectancy to $<$6 months, were participating in a device study, had preoperative use of a balloon pump, inotropes/vasopressor drugs or treatment for pulmonary arterial hypertension, had known hypersensitivity to tezosentan or other ERAs, or had severe liver impairment.

Eligible patients were randomized (1:1) to receive either tezosentan via intravenous infusion, administered at 5 mg/h from the start of surgery (chest incision) to the end of surgery (chest closure) and 1 mg/h thereafter for up to 24 hours (total infusion) or a matching placebo infusion. If pulmonary pressures increased after the discontinuation of study treatment, study treatment could be reinstated at 1 mg/h and continued for up to 72 hours (total infusion) if the investigator felt that this was warranted. During the 5 mg/h infusion, the rate could be decreased to 1 mg/h if the patient had not responded to standard care for hypotension. The dose selection for the current study was based on observations made in previous trials[10,15] and dose titration studies.[9] Concomitant medications were permitted according to local standards of care with the exception of prophylactic treatment of perioperative PH, prophylactic intravenous vasopressor/inotropic treatment before CPB (although a bolus of milrinone was permitted before cross-clamp release if considered warranted), cyclosporine A, or tacrolimus.

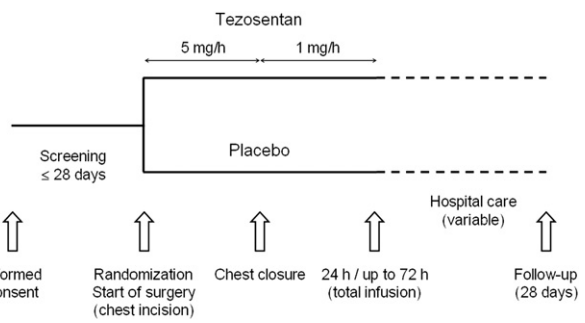

Fig 1. Study design.

Study Endpoints

Efficacy Endpoints

The primary efficacy endpoint was the proportion of patients who experienced clinically relevant RV failure during weaning from CPB. The definition of clinically relevant RV failure required a consensus between the cardiac surgeon and the cardiac anesthesiologist. Clinically relevant RV failure was defined using 3 inclusive criteria: (1) hemodynamic instability defined as a requirement for the use of $\geq$3 inotropic/vasopressor treatments or 2 at high doses (dopamine $>$5 μg/kg/min; dobutamine $>$5 μg/kg/min; norepinephrine $>$0.05 μg/kg/min; epinephrine $>$0.05 μg/kg/min; milrinone $>$0.5 μg/kg/min; phenylephrine $>$2.5 μg/kg/min; isoproterenol $>$0.01μg/min; vasopressin at a cumulative dose of $>$10 units; levosimendan $\geq$0.2 μg/kg/min), or return to CPB for hemodynamic instability or use of rescue therapy for high pulmonary arterial pressure (defined as mean pulmonary artery pressure $>$50 mmHg or systolic pulmonary artery pressure $>$60 mmHg), or use of ventricular assist device or death (all causes); (2) echocardiographic criteria defined as severe reduction of RV fraction area change ($>$20%) measured by two-dimensional echocardiography; and (3) anatomic visualization defined as significant reduction or absence of RV wall motion by direct visual inspection intraoperatively. The primary endpoint was assessed 30 minutes after the end of CPB or, for death, up to 24 hours after the start of weaning from CPB.

Secondary efficacy endpoints were the proportion of patients with a major clinical event within 28 days, time to weaning from CPB (ie, from release of cross-clamp to successful weaning from CPB) and time from end of CPB to final discharge from the intensive care unit. Major clinical events were death, major cardiovascular event (acute pulmonary edema, myocardial infarction, stroke, ventricular arrhythmia requiring cardioversion, cardiogenic shock, or cardiac arrest), infection that prolonged the hospital stay or required readmission, new onset of renal failure requiring renal replacement therapy, and the degree of separation from CPB classified as easy (1 vasoactove agent), difficult (2 classes of drugs), and complex (requiring surgical intervention).[16]

Safety Endpoints

Safety endpoints were treatment-emergent adverse events (AEs) (AEs occurring from the start of study treatment up to 48 hours after the end of study treatment), deaths occurring from the start of study treatment up to 24 hours after weaning from CPB, treatment-emergent serious AEs (SAEs), and AEs leading to permanent discontinuation of study treatment. Adverse events were graded on a 3-point scale (mild, moderate, and severe).

Statistical Methods

The main analyses of the primary and secondary efficacy endpoints were conducted on the all-treated set (all randomized patients who received study treatment, independent of the extent or duration of

exposure). A total of 270 patients, randomized 1:1 to receive tezosentan or placebo, was required for the study to have 90% power to detect a relative risk reduction of 40% in the incidence of RV failure in the active treatment group from an expected incidence of 50% with placebo (ie, an incidence of 30% with active treatment). Continuous variables are expressed as mean ± SD, and their differences were tested with the two-sample t test. Categorical variables are expressed as frequencies and percentages; and their differences were tested with the χ^2 test if the size of the cell was >5, otherwise the Fisher exact test was used. The primary endpoint was analyzed by comparing the incidence of RV failure with tezosentan to placebo (relative risk reduction) by means of the χ^2 test at a 0.05 (two-sided) significance level without adjustment for covariates. Its 95% confidence interval (CI) also is presented. Time-to-event endpoints were analyzed using the Kaplan-Meier (K-M) technique, with treatment effect evaluated as the hazard ratio provided with the p value from the log-rank test. Safety and tolerability were analyzed on the safety set. All analyses were done with SAS version 9.2 and conducted at the 0.05 significance level.

RESULTS

Disposition of Patients

The study was conducted at 31 centers in 14 countries: Austria (2 centers), Canada (5), Czech Republic (1), France (1), Germany (3), India (2), Israel (1), Italy (2), Poland (1), Serbia (1), Slovakia (1), Sweden (1), the United Kingdom (2), and the United States (8).

A total of 284 patients were randomized to tezosentan (n = 139) or placebo (n = 145). Ten randomized patients (tezosentan, n = 6; placebo, n = 4) did not receive study treatment. Hence, the all-treated set comprised 274 patients (tezosentan, n = 133; placebo, n = 141). All of these patients also had at least one post-baseline safety assessment. Therefore, the all-treated and safety analysis sets were identical. The overall disposition of the patients is presented in Fig 2; patients who completed the 24-hour treatment period and those who discontinued study treatment prematurely were followed-up for 28 days and were considered to have completed the study. The treatment groups in the all-treated analysis set were generally well matched with respect to demographics, planned cardiac surgery, and baseline characteristics (Table 1).

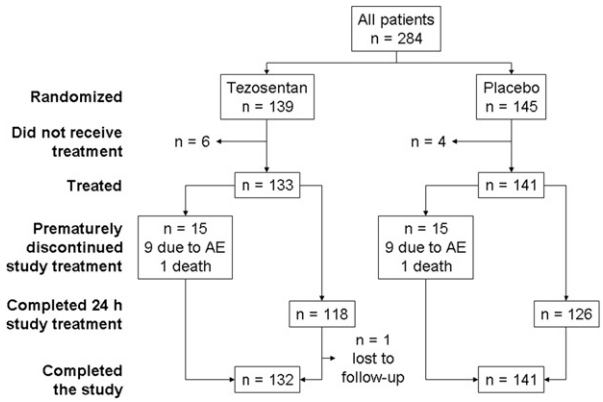

Fig 2. Disposition of patients.

Efficacy

A total of 30 (10.9%) patients developed RV failure from which 11 died (37%). No significant difference was observed with respect to the primary endpoint between the two treatment groups: 14 patients in the tezosentan group (10.5%) compared with 16 patients in the placebo group (11.3%) had RV failure during weaning from CPB. This represented a relative risk reduction =0.07 [95% CI −0.83, 0.53]; p = 0.8278). The specific events that denoted RV failure also were comparable between the 2 groups (Table 2), with several patients having more than one qualifying event. In terms of specific drugs used during CPB weaning, there were no differences between the groups. Intravenous milrinone was administered in 49 patients (34.8%) in the placebo and 38 (28.6%) in the tezosentan group; nitric oxide was used in 1 patient in the placebo and 2 patients in the tezosentan group. No patients received inhaled prostacyclin or inhaled milrinone. Only intra-aortic balloon pumps were used as assist devices, and 1 patient in the tezosentan group required extracorporeal membrane oxygenation postoperatively.

Six patients developing RV failure (n = 11), who died, required return on CPB or required an intra-aortic balloon pump. The cause of death in patients developing RV failure was multisystem organ failure in 7 patients (4 in placebo and 3 in tezosentan). In the placebo group, 2 patients had major cardiovascular instability complicated by uncontrolled mediastinal hemorrhage and ventricular fibrillation. In the tezosentan group, 1 patient developed refractory biventricular failure, and another patient died of a cerebrovascular accident that was associated with significant hemodynamic instability. Three additional patients with RV failure developed severe adverse events, including acute renal failure and significant infections resulting in prolonged hospitalization. In those patients who died (n = 24), 3, 12, and 9 experienced easy, difficult, and complex separation from CPB, respectively.

No treatment effects with tezosentan compared with placebo were observed for the secondary endpoints. In each of the groups, 24.1% of patients had a major clinical event within 28 days of study treatment and K-M estimates for time to successful weaning from CPB and time from the end of CPB to final discharge from the intensive care unit were comparable (Table 3).

Safety

The mean duration of exposure to study treatment was similar in the 2 treatment groups (22.7 h and 23.2 h in the tezosentan and placebo groups, respectively), and 82.7% of patients in the tezosentan group and 81.6% of patients in the placebo group received at least 24 hours of study treatment. More than 90% of patients in both groups received vasoactive support (tezosentan, 98.5%; placebo, 97.9%).

Treatment-emergent AEs were comparable between the 2 groups, occurring in 73.7% of patients in the tezosentan group and 71.6% of patients in the placebo group. There were no statistical differences between the groups. Adverse events with a higher incidence on tezosentan than placebo (≥4% difference) included hypotension, atrial fibrillation, anemia, acute renal failure, and thrombocytopenia. Only anemia was more common in the tezosentan group than placebo (15% v 7.1%, p = 0.0353). Most treatment-emergent AEs were of mild-to-

Table 1. Summary of Baseline Characteristics and Patient Demographics (All-treated Set)

	Tezosentan (n = 133)	Placebo (n = 141)	*P* value
Male, n (%) / Female, n (%)	75 (56.4) / 58 (43.6)	88 (62.4) / 53 (37.6)	0.3103
Age, years			0.8673
Mean ± SD	64.2 ± 14.0	64.5 ± 15.6	
Range	21.0–86.0	19.0–87.0	
Weight, kg			0.5023
Mean ± SD	72.2 ± 17.9	73.6 ± 16.6	
Range	39.0–117.1	36.0–112.0	
Ethnic origin, n (%)			0.9195
White	110 (82.7)	115 (81.6)	
Black	2 (1.5)	3 (2.1)	
Asian	19 (14.3)	22 (15.6)	
Hispanic	2 (1.5)	1 (0.7)	
Complex surgery, n (%)			0.8967
Yes	113 (85.0)	119 (84.4)	
No	20 (15.0)	22 (15.6)	
Cardiovascular parameters, mmHg			
SBP, mean ± SD (range)	126.8 ± 19.1 (100.0–200.0)	128.5 ± 19.6 (100.0–190.0)	0.4682
DBP, mean ± SD (range)	72.4 ± 11.1 (48.0–110.0)	71.3 ± 11.8 (38.0–100.0)	0.4281
sPAP*, mean ± SD (range)	62.4 ± 15.9 (40.0–122.0)	63.6 ± 15.7 (40.0–115.0)	0.5339
mPAP†, mean ± SD (range)	42.7 ± 10.1 (20.0–68.0)	43.1 ± 11.9 (15.0–70.0)	0.8552

Abbreviations: DBP, diastolic blood pressure; mPAP, mean pulmonary artery pressure; SBP, systolic blood pressure; SD, standard deviation; sPAP, systolic pulmonary artery pressure.

* Tezosentan, n = 132; placebo, n = 137.

† Tezosentan, n = 46; placebo, n = 60.

moderate intensity, but at least one severe event was reported in 26.3% and 19.9% of patients in the tezosentan and placebo groups, respectively. Most treatment-emergent AEs were considered to be unrelated to study treatment. Only hypotension was considered to be related to study treatment in more than 2 patients in either treatment group (tezosentan, n = 17 [12.8%]; placebo, n = 15 [10.6%]). The overall incidences of treatment-emergent SAEs were comparable in the tezosentan (36.1%) and placebo groups (37.6%).

DISCUSSION

The current study was unable to demonstrate a significant benefit of an infusion of tezosentan during cardiac surgery in reducing the incidence of RV failure during weaning from CPB in patients with PH due to left-sided heart disease. Right ventricular failure was less common than expected; however, it is still associated with increased risk of mortality as more than one third of those patients will die. This is the largest study to date reporting the actual incidence of this complication in an international multicenter study. In addition, more than half of the patients with RV failure had complex separation from CPB, and 87.5% of those who died experienced difficult or complex separation from CPB. This is consistent with another study of 2331 high-risk patients in which 77.8% of those who died experienced difficult or complex separation from CPB.[16]

The expected event rate for RV failure leading to difficult weaning from CPB among placebo-treated patients with significant PH was higher than what was observed. This predicted event rate was unknown and therefore based on clinical experience from the Montreal Heart Institute database of cardiac surgery.[17,18] On the basis of the study by Robitaille et al,[17] at least 40% patients with the degree of PH that we observed in our study would have been expected to develop significant postoperative hemodynamic complications. However, the observed event rate with placebo in the present study was substantially lower at 11%. The reasons for discrepancy compared with the anticipated event rate are unknown but could be related to changes in practice since those estimations were obtained, variation in the definition of RV failure between centers, and differences between the patient populations in this study and that on which the power analysis was based.

Table 2. Summary of Events Denoting Right Ventricular Failure during Weaning from CBP (All-treated Set)

	Tezosentan (n = 133)	Placebo (n = 141)	*P* value
Patients with at least one event, n (%)	14 (10.5)	16 (11.3)	0.8278
≥3 vasopressors	8 (6.0)	10 (7.1)	0.7191
≥2 vasopressors at high dose	6 (4.5)	7 (5.0)	0.8600
Rescue therapy for high PAP	3 (2.3)	4 (2.8)	1.000
Return to CPB	4 (3.0)	3 (2.1)	0.7160
Use of assist devices	5 (3.8)	2 (1.4)	0.2703
Death within 24 h from start of weaning	1 (0.8)	2 (1.4)	1.000

Abbreviations: CPB, cardiopulmonary bypass; PAP, pulmonary artery pressure.

Table 3. Summary of Secondary Efficacy Endpoints (All-treated Set)

	Tezosentan (n = 133)	Placebo (n = 141)	*p* value
Patients with ≥1 major clinical event, n (%)	32 (24.1)	34 (24.1)	0.9918
Infections*	14 (10.5)	14 (9.9)	0.8704
Death	14 (10.5)	10 (7.1)	0.3149
Major cardiovascular event	10 (7.5)	14 (9.9)	0.4806
New onset of renal failure†	5 (3.8)	6 (4.3)	0.8344
Loss to follow-up	1 (0.8)	–	0.4854
K-M estimate of time to weaning from CPB			
Hazard ratio	0.939		
95% CL of hazard ratio	0.740, 1.192		
Logrank *p* value	0.597		
K-M estimate of time from end of CPB to ICU discharge			
Hazard ratio	0.836		
95% CL of hazard ratio	0.659, 1.062		
Logrank *p*-value	0.090		

Abbreviations: CL, confidence limits; CPB, cardiopulmonary bypass; ICU, intensive care unit; K-M, Kaplan-Meier.

* Prolonging hospital stay or requiring readmission.

† Requiring replacement therapy.

Primary and secondary endpoint results did not indicate a treatment effect of tezosentan. The absence of a treatment effect was unlikely to have been due to deviations from the protocol-specified procedures, as the results of the analysis on the per-protocol set were nearly identical to those of the main analysis. In addition, no baseline imbalances between treatment groups were evident.

As in previous studies,[15] higher incidences of hypotension and renal failure were observed with tezosentan than with placebo. Hypotension led to premature discontinuation, in a few patients in each group. Also observed in this study were higher incidences of anemia, atrial fibrillation, complete atrioventricular block, multi-organ failure, thrombocytopenia, and decreased oxygen saturation with tezosentan than placebo. In the context of cardiac surgery, with the inherent blood loss and fluid replacement, it is difficult to ascertain what may have contributed to the occurrence of these events. With higher doses of tezosentan, decreased hemoglobin was observed in patients hospitalized with acute decompensated heart failure,[19] and an increased incidence of atrial fibrillation was reported in patients with acute pulmonary edema.[20] Thus tezosentan may have contributed to the occurrence of some of these events in this study population despite the current dosage used.

It also is possible that tezosentan might not be well tolerated in patients with secondary PH due to left ventricular dysfunction as opposed to those with PH secondary to valvular dysfunction. Similar to results seen with nitric oxide,[21] the improvement in RV afterload with these agents can be followed by an increase in left ventricular preload and filling pressure. This also could explain why the previous trials on tezosentan were negative in the heart failure population. In this study, we did not measure pulmonary capillary wedge pressure during tezosentan administration, which could have given more insight on this potential detrimental side effect.

Prevention of postoperative RV failure in a large clinical trial of patients undergoing cardiac surgery has not been performed before. However, there have been several small randomized clinical trials in cardiac surgical patients with PH.[22] In these trials, most of the end-points were, however, limited to the reduction in the severity of PH and not necessarily the prevention of RV failure.

Other limitations of the study include the diagnosis of RV failure. RV dysfunction was defined based on hemodynamic, echocardiographic, and anatomic criteria. Echocardiographic study of the right ventricle is more challenging than that of the left, and guidelines were published in 2010 on the echocardiographic evaluation[23] before the trial was designed. The main difficulties encountered may be explained by the complex RV shape, heavy apical trabeculations, which limits endocardial surface recognition, and the marked load dependence of several indices of RV function. This explains why we did not rely only on two-dimensional measurements, but we needed the presence of significant hemodynamic instability, which is an hallmark of RV failure and also a consensus between the anesthesiologist and the cardiothoracic surgeon.

It also is possible that postoperative PH also is not uniquely ET dependent and other pathways such as nitric oxide- and prostacyclin-mediated pathways might be operating,[24] the relative importance of these pathways being variable. Consequently, combination therapy using vasodilators, anti-inflammatory and inhalation therapy might be more efficacious than targeting a single mechanism, as is the case in pulmonary arterial hypertension. In addition, severe RV failure after CPB also can be the result of many inciting events that would increase pulmonary vascular resistance, such as atelectasis, pneumothorax, volume overload, valvular mechanisms, coronary malperfusion or embolism, and inadequate time given for weaning from CPB. Prevention of pulmonary reperfusion injury and specific pulmonary vasodilatation through endothelin blockade would not address all these potential etiologies.

CONCLUSIONS

In this study of patients undergoing cardiac surgery with significant PH, RV failure occurred in 10.9% of patients, 37% of whom died. A decrease in the relative risk of RV failure

during weaning from CPB was not observed with a 24-hour infusion of tezosentan compared with placebo.

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