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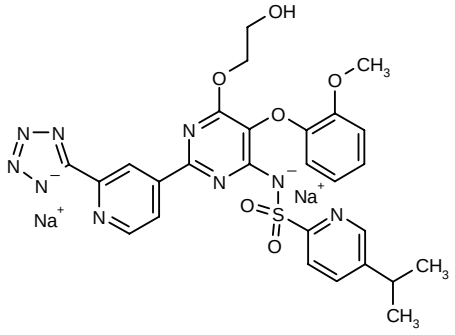
Tezosentan Disodium

Treatment of Heart Failure

Prop INNM

Ro-61-0612
Veletri™

N-[6-(2-Hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)pyridin-4-yl]pyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide disodium salt



EN: 279345

CAS: 180384-58-1

CAS: 180384-57-0 (as free acid)

Abstract

The involvement of endothelin in the pathogenesis of heart failure is well known. Endothelin acts to increase vasoconstriction, as well as having effects on the contractility and proliferation of heart tissue. The clinical benefit of the type and degree of endothelin receptor blockade, however, has not yet been elucidated. Tezosentan is a mixed endothelin receptor antagonist developed specifically for parenteral administration and is indicated for the treatment of heart failure. While early clinical trials showed tezosentan to improve the hemodynamics in patients with heart failure without affecting ischemic burden or risk of increased heart rate or arrhythmia, more recent results have shown that the drug does not improve survival or reduce the frequency of worsening heart failure, and is associated with a higher incidence of renal failure. Therefore, careful analysis must now be undertaken to properly establish the efficacy and tolerability of tezosentan within this context.

Synthesis

Reaction of 4-cyanopyridine (I) with Na in methanol followed by treatment with ammonium chloride provides 4-amidinopyridine hydrochloride (II), which is then converted into 5-(2-methoxyphenoxy)-2-(pyridin-4-yl)pyrimidine-4,6-diol (IV) by condensation with the diethyl malonate derivative (III) by means of Na in MeOH. By heating compound (IV) with phosphorus oxychloride ($POCl_3$), 4,6-dichloro-5-(2-methoxyphenoxy)-2-(pyridin-4-yl)pyrimidine (V) is obtained, which is oxidized with peracetic acid in refluxing acetonitrile to afford the *N*-oxide derivative (VI). Alternatively, reaction of 2-chloro-5-ispropylpyridine (VII) with thiourea in aqueous HCl gives 5-isopropylpyridine-2-thiol (VIII), which is chlorinated with chlorine in acetic acid to yield 5-isopropylpyridine-2-sulfochloride (IX). This compound is converted into 5-isopropylpyridine-2-sulfonamide potassium salt (X) by treatment first with aqueous ammonium hydroxide and then with potassium hydroxide or alkoxide. Condensation of the *N*-oxide derivative (VI) with the sulfonamide potassium salt (X) furnishes 5-isopropylpyridine-2-sulfonic acid 6-chloro-5-(2-methoxyphenoxy)-2-(1-oxy-pyridin-4-yl)pyrimidin-4-yl amide (XI), which is then dissolved in dimethoxyethane and subjected to reaction with Na in hot ethylene glycol (XII) to provide *N*-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(1-oxy-pyridin-4-yl)pyrimidin-4-yl]-5-isopropylpyridine-2-sulfonamide (XIII). Refluxing compound (XIII) with trimethylsilylcyanide and Et_3N in acetonitrile yields the cyano derivative (XIV), which is then converted into the tetrazole derivative (XV) by reaction with sodium azide and NH_4Cl in DMF at 70 °C. Finally, the disodium salt of tezosentan is obtained by treatment of compound (XV) with NaOH/MeOH in THF (1, 2). Scheme 1.

Introduction

Heart failure describes the pathophysiologic state whereby the heart can no longer pump enough blood to

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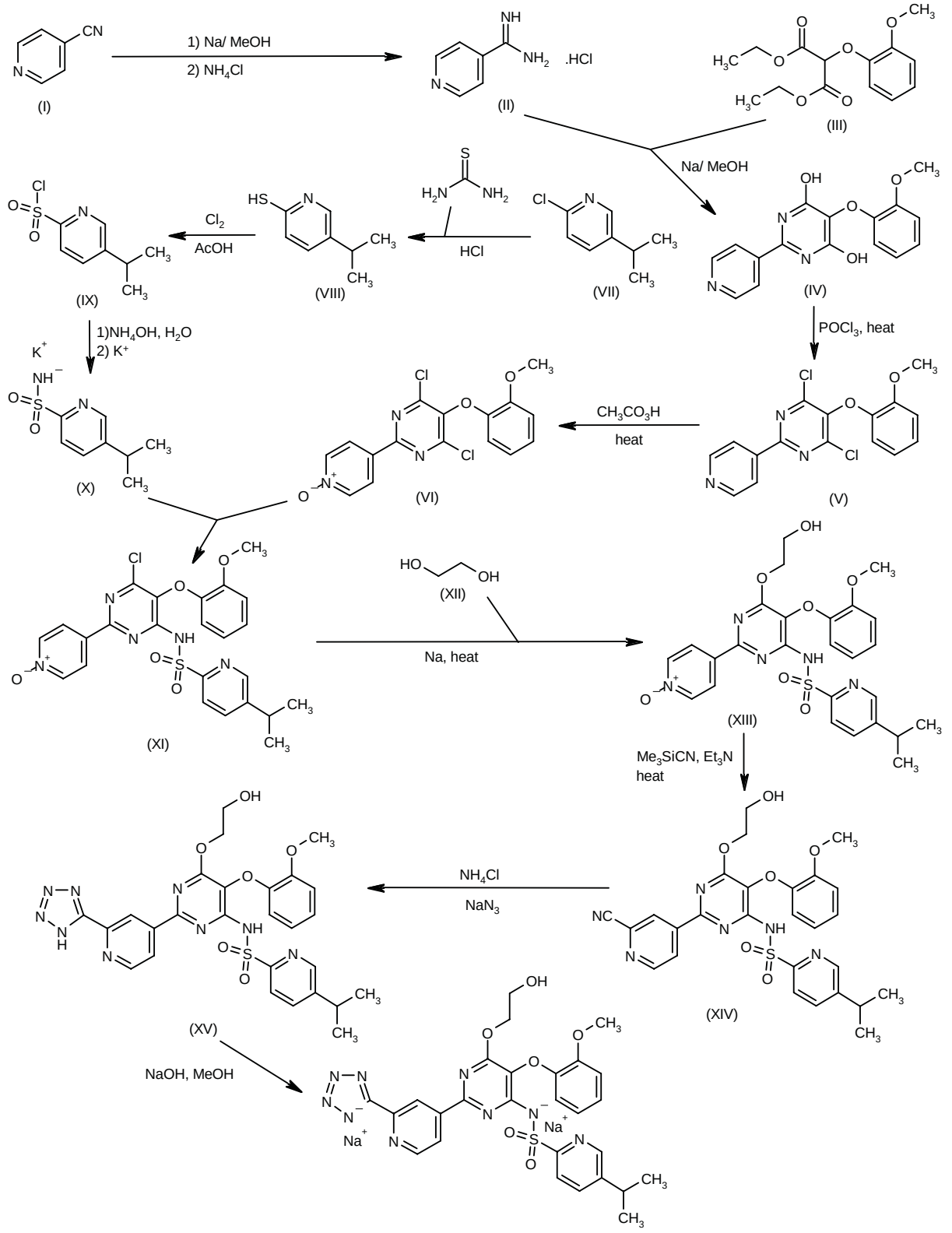
Scheme 1: Synthesis of Tezosentan Disodium



supply the body's demands. Pump failure is preceded by an insult to the myocardium rendering it unable to contract effectively. This reduction in cardiac contractility results in a decreased cardiac output, leading to a reduced delivery of oxygen and nutrients to body tissues. These disturbances can ultimately lead to cardiovascular collapse and death (3).

Heart failure is the end stage of a number of diseases affecting the heart and is a consequence of increased cardiac overload leading to myocardial wall stretching, ultimately resulting in ventricular hypertrophy. It is a progressive condition, but can also present acutely following an exacerbation of an already chronic underlying disease. There are many different causes of heart failure, including myocardial damage, volume overload, obstruction to outflow, compromised atrial filling and arrhythmia. Acute heart failure shares many of the characteristics associated with chronic heart failure, however the process occurs over a shorter period of time, and is subsequently much more exaggerated (4).

Heart failure can manifest itself through a number of clinical and hemodynamic signs/symptoms including tachycardia, reduced arterial pressure, increased venous pressure, exercise intolerance and dyspnea. Heart failure presents insidiously in most cases, with dyspnea often being the only symptom experienced by patients. Heart failure is a major cause of morbidity and mortality, with only 50% of patients with severe heart failure surviving at 1-year. The prevalence of the condition is rising worldwide, with an increase of 160% being reported over the last 2 decades. These increases prevail despite advances in research into therapeutic management of this common condition. The incidence of heart failure rises with age, therefore the increased incidence is thought to be due at least in part to the effects of the aging population (5).

Heart failure treatment is generally aimed at stabilizing the patient and providing them with symptom relief. Currently available therapies for heart failure include pharmacological agents that possess 3 important basic mechanisms of action; namely inotropes, diuretics and vasodilators. ACE inhibitors, angiotensin II receptor antagonists, β-receptor blockers, aldosterone receptor antagonists, dopamine and digoxin are some of the more commonly used heart failure therapies. There are significant limitations with these kinds of treatments, however, as they do not target the actual disease process *per se*. Pharmacological agents given to interrupt the pathophysiological sequence of events that ultimately results in a failing heart are not routinely used in clinical practice but are very much needed in this setting (6, 7).

The role of endothelin in heart failure

The vascular endothelium is responsible for the production and release of a number of vasoconstrictors that work to regulate vascular tone. Endothelin (ET) is one such vasoconstrictor peptide and is synthesized both by vascular endothelial cells and cardiac myocytes. It is the most potent long-acting endogenous vasoconstrictor reported to date. It regulates blood pressure through action at receptor sites on both arteries and veins and is released during episodes of ischemia (8).

Discovered in 1988, the endothelin system plays a complex and diverse role in multiple disease states. Endothelin has been purported to play a role in a number of important pathological processes including atherosclerosis, hypertension, myocardial infarction and chronic renal failure (9).

The specific role of endothelin in the pathophysiology of heart failure is well recognized. The endothelin system has been shown in many instances to be increased in both clinical and experimental studies of heart failure. Endothelin production is increased in animal models of heart failure, as is the expression of its endothelin receptors. These elevations in endothelin levels are strongly related to survival in this context (10).

Changes to the endothelin system in animals with heart failure are mirrored by changes in patients with this condition. Elevated tissue and serum levels of ET_1 are found in patients with heart failure. Receptor density is also upregulated in these patients. Response to endothelin levels is also changed in the failing compared with the normal heart. ET_B receptor activation is increased, while ET_A receptor activation is diminished, leading to a greater vasoconstrictor response in heart failure. Tissue and serum endothelin levels are raised in patients with heart failure. A linear relationship exists between endothelin levels and symptom severity in such patients. Endothelin levels have been shown to be predictive of cardiac performance and degree of the pulmonary hypertension characteristic of heart failure. Moreover, endothelin is closely correlated with measures of prognosis and conversely with mortality in patients with heart failure. Raised endothelin levels also reduce the ability of the vasculature to dilate during exercise, thereby predisposing the patient to the exercise intolerance characteristic of heart failure (11, 12).

Endothelin affects the pathogenesis of heart failure in two ways. Firstly, endothelin increases the contractility of myocytes and endothelial cells. Endothelin also has long-term cardiac tropic influence on cardiac muscle, leading to the ventricular hypertrophy and cardiac remodeling indicative of heart failure. Therefore, endothelin is important in heart failure not only as a powerful vasoconstrictor but also because it plays a central role in the cellular proliferation that commonly accompanies heart failure pathology (13).

Endothelins comprise a family of three isoforms, ET_1, ET_2 and ET_3. Each isoform contains 21 amino acids. ET_1 is the endothelin isoform responsible for cardiovascular symptoms and has been implicated specifically in the pathogenesis of heart disease. ET_1 plays a role in the regulation of vascular tone and has been associated with salt and water homeostasis. ET_1 also has positive inotropic and mitogenic properties (14).

The vasoconstrictor and proliferative effects of endothelin are mediated via interaction at two known G-protein-coupled receptor sites, ET_A and ET_B. These endothelin receptors are found in brain, heart, lung and mesangial cells. The function of the receptor subtypes depends on where they are located. In this way, ET_A receptors stimulate vasoconstriction when they are located in vascular beds, yet have tropic effects and cause contractility of the heart in myocytes. Activation of ET_B receptors leads to vasodilation regardless of their location. ET_A has a high binding affinity for ET_1 and ET_2, while ET_B binds all isoforms equivalently (15).

With the role of endothelin receptor activation being clearly defined in the pathogenesis of heart failure, attention has turned to the development of drugs that can block activity at these sites. A number of pharmacological agents targeted to antagonizing either ET_A, preferentially, or ET_A/ET_B are currently being developed (16).

Endothelin receptor antagonists

Endothelin receptor antagonists represent a novel therapeutic approach to the treatment of both chronic and acute heart failure. The rationale for the development of endothelin receptor antagonists was to design a class of drug that blocks the vasoconstriction, hypertrophy and neurohormonal activation characteristic of endothelin action. In this way, while other drugs are aimed at symptomatic relief in heart failure, endothelin receptor antagonists are directed towards reversing the disease process (17, 18).

Endothelin has been observed to exert differential effects on myocardial contractility in the normal compared with the failing heart. While endothelin exerts a positive inotropic effect in the normal heart, it is purported to have a negative inotropic effect in failing myocardium. In this way, endothelin receptor antagonists paradoxically increase myocardial contractility in the failing heart (11).

Mixed ET_A/ET_B receptor antagonists are preferred in the treatment of congestive heart failure, as blockade of both receptor subtypes is needed to inhibit pulmonary hypertension. Mixed antagonists, therefore, share the hemodynamic effects of ET_A receptor antagonists but incur extra benefit in their ability to prevent fluid retention (19, 20).

There have been reports of endothelin receptor antagonists having a deleterious effect on cardiovascular function. Endothelin receptor antagonists have been shown to improve or worsen cardiac function depending on the loading condition of the heart. Cardiac performance is enhanced by decreasing peripheral vascular resistance. Blockade of the endothelin system may also impair adaptation of the heart to increased load, therefore leading to an early exacerbation of heart failure. Concerns, therefore, remain regarding the safe use of these pharmacological agents in some settings (21).

Bosentan was the first member of this therapeutic class to have been approved by the U.S. FDA for the treatment of congestive heart failure. Bosentan is an orally active mixed ET_A/ET_B receptor antagonist and is used more specifically in patients with stable heart failure. Results from a recently conducted multicenter, double-blind, placebo-controlled trial showed that bosentan is a safe and effective oral treatment for patients with chronic heart failure. The long-term benefits of bosentan have not yet been studied. Results from such studies led researchers to develop tezosentan, an intravenous form of the mixed ET_A/ET_B receptor antagonist for use in patients who present acutely as opposed to those with chronic, stable disease (22).

Pharmacological Actions

Tezosentan is a novel, potent, highly specific endothelin receptor antagonist. Tezosentan acts as a competitive antagonist at endothelin receptor binding sites and, therefore, its antagonistic potential is dependent on serum concentrations of the drug. While tezosentan has a high affinity for both ET_A and ET_B receptor subtypes, it binds preferentially to ET_A. Tezosentan antagonized the specific binding of radiolabeled ET_1 to ET_A and ET_B with a K_i of 0.3 nM and 10-21 nM, respectively. Thus, tezosentan displays a binding potency 30 times greater with ET_A over ET_B receptor subtypes (23).

Action at both of these sites gives tezosentan a differential role in both vasodilation and vasoconstriction, depending on the location of the endothelin receptor sites. Tezosentan binds preferentially to ET_A, however, resulting in an overall effect of producing vasodilation. This vasodilatory action works to decrease vascular resistance, thereby leading to a reduction in the afterload normally indicative of heart failure (24).

Studies in animal models of heart failure unanimously show that inhibition of endothelin is associated with an improvement in hemodynamic conditions.

Tezosentan was very effective in the treatment of rats with experimental congestive heart failure. In a commonly used animal model of heart failure, rats underwent left coronary artery ligation to imitate myocardial infarction and developed congestive heart failure in the following weeks. Hemodynamic response was measured via mean arterial pressure (MAP - an indicator of overload). MAP was decreased in tezosentan compared with control animals. This change was observed in the absence of other alterations in heart rate (HR) or cardiac contractility. Tezosentan significantly decreased left ventricular end diastolic pressure (LVEDP - an indicator of preload). These favorable hemodynamic effects were shown to be comparable to those of the commonly administered ACE inhibitor enalapril (25).

Tezosentan is thought to play a role in the regulation of the altered renal hemodynamics associated with heart failure. Results from a recently conducted animal study showed that tezosentan reversed the renal vasoconstriction characteristic of heart failure. Male normotensive rats with experimental congestive heart failure were assessed

Table I: Tezosentan pharmacokinetics after single i.v. administration in different animal species and adult human males.

Animal species	Dose (mg/kg)	C_{max} (mg/l)+	$t_{1/2}$ (h)	Cl (ml/min/kg)	V_{ss} (l/kg)	Ref.
Rats	10	94.3	2.1	4.3	0.3	23
Rabbits	5	11.4	0.4	34.3	0.4	23
Monkeys	10	39.6-82.8	0.5-0.8	10.0-19.3	0.1-0.3	23

Humans	Dose (g)	C_{max} (mg/l)	AUC_{∞} (mg·h/l)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Cl (l/h)	V_{ss} (l)	Ref.
	0.005 1 h	0.1	0.1*	0.1	-	-	-	28
	0.02 1 h	0.3	0.3*	0.1	-	-	-	28
	0.05 1 h	1.2	1.0	0.1	2.7	49	16	28
	0.1 1 h	3.0	2.9	0.1	3.4	36	19	27, 28
	0.2 1 h	7.9	7.1	0.1	3.9	28	22	28
	0.4 1 h	23	19	0.2	3.5	21	10	28
	0.6 1 h	26	23	0.2	2.9	26	13	28

+C_{max}: plasma concentration at 5 min postdosing. *AUC until the last time point with measurable concentration.

for renal impairment as measured via renal vascular resistance (RVR), renal plasma flow (RPF) and glomerular filtration rate (GFR). Rats underwent coronary artery ligation 3-5 weeks prior to the investigation. Tezosentan decreased RVR by 43% compared with baseline and RPF and GFR were significantly increased. It was concluded that tezosentan significantly alters renal hemodynamics in rats with experimental heart failure. The implications for use within a clinical setting were not discussed; however, it was acknowledged that tezosentan could potentially have an effect on renal as well as the cardiovascular function in humans (13).

A later study further underlined the role of tezosentan in the regulation of kidney function. Pre- and posttreatment with tezosentan was associated with improved renal hemodynamics in rats undergoing experimental renal ischemia. Serum creatinine levels were significantly decreased, while GFR was simultaneously increased. Renal histology as well as renal function was preserved following tezosentan administration in this analysis (26).

Results from *in vivo* analyses showed tezosentan to dose-dependently inhibit the effects of endothelin through blockade of the receptor sites, while also bringing about a concurrent increase in endothelin levels themselves. Blockage of endothelin receptors, therefore, results in an increased level of circulating endothelin. Thus, safety concerns have arisen in that following withdrawal of treatment, a rebound effect may take place, where increased endothelin levels result in a worsening of heart failure status.

Pharmacokinetics

A total of 56 healthy male volunteers took part in an ascending single-dose study of tezosentan. Subjects were administered radiolabeled tezosentan 5-600 mg i.v. for 1 h in this randomized, double-blind, placebo-controlled trial and plasma endothelin concentrations were measured up to 15 h postinfusion. The pharmacokinetic profile of tezosentan displayed characteristics indicative of a two-compartment model of elimination. Plasma concentrations of tezosentan decreased rapidly following discontinuation of the i.v. infusion. Elimination rates exhibited a biphasic profile. Tezosentan was metabolized at a very low rate, with small amounts of 2 metabolites being identified (M_1 and M_2). These accounted for less than 5% of the total tezosentan dose and were therefore overlooked in the majority of the analyses. Tezosentan was excreted largely unchanged in the feces, with only 5% being excreted in the urine (27, 28). The pharmacokinetics of single-dose tezosentan are shown in Table I.

Tezosentan has a short half life (10-12 min), meaning that rapid titration of its effects can be facilitated. This short half-life also allows for a plateau effect to be reached rapidly, which can then easily be adjusted. Tezosentan is optimized for i.v. administration due to its water solubility, potency and short $t_{1/2}$. All of these features also make tezosentan an ideal candidate for the treatment of heart failure in an acute situation, the setting for which it was designed (23, 29).

Concomitant administration of ciclosporin with tezosentan in 12 healthy male volunteers exhibited a pharmacokinetic interaction. The AUC and C_{max} of tezosentan were increased up to 4-fold with concurrent treatment with ciclosporin, whereas values for systemic plasma clearance (Cl), percentage of dose recovered in urine (UR) and volume of distribution at steady sate (V_{ss}) decreased 3- to 4-fold. The $t_{1/2}$ and renal clearance (Cl R) values were not affected. This interaction resulted in decreased elimination and a subsequent increase in tolerability profile. The concomitant administration of these drugs is therefore contraindicated in clinical practice (30) (Fig. 1).

Clinical Studies

Initial clinical studies assessing the effects of tezosentan in patients with heart failure produced promising results for the dual endothelin receptor antagonist candidate.

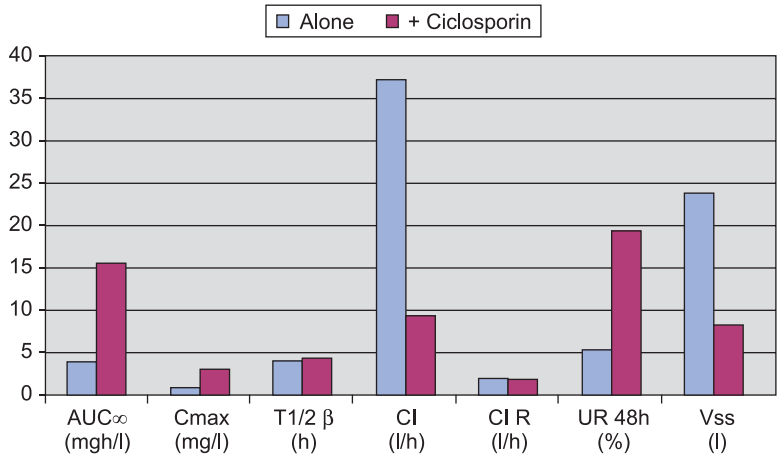


Fig. 1. Pharmacokinetic parameters of tezosentan (150 mg i.v.) alone or in combination with ciclosporin (400 mg) in humans (ref. 30).

Two phase II dose-finding studies were carried out in patients with moderate to severe chronic heart failure to determine the dose-effectiveness of tezosentan. Short-term infusions (over 4-6 h) of tezosentan 5-100 mg/h were administered in both studies (31-37).

In the first study, the hemodynamic effects of tezosentan were assessed in a group of patients with chronic heart failure using a randomized, double-blind, placebo-controlled trial design. A total of 61 patients aged 18-70 years with NYHA class III-IV heart failure were included in this analysis. Patients were randomized to receive an infusion of placebo or tezosentan 5, 20, 50 and 100 mg/h for 6 h. All patients were receiving established medications for heart failure, including an ACE inhibitor and a diuretic. The primary outcome variable in this study was cardiac index (CI). CI is a typical hemodynamic parameter used to measure treatment response in patients with heart failure. It describes the amount of blood pumped by the heart per minute/body surface area. CI does not accurately predict other indicators of a failing heart including exercise intolerance or long term prognosis; however, it is routinely used and can therefore be used to compare different therapies between studies. Cardiac output (CO), pulmonary capillary wedge pressure (PCWP) and pulmonary artery pressures were also determined. CI and other hemodynamic variables were measured every 30 min throughout the duration of the infusion. Results showed that tezosentan administration was associated dose-dependently with an increase in CI. Change from baseline in CI score was reported to be 26.9%, 24.4%, 30.9% and 49.9% following infusion of tezosentan 5, 20, 50 and 100 mg/h at 6 h postadministration. There were no changes from baseline observed following placebo administration. Effects were observed after only 30 min, with a maximum effect being reported at 90-120 min. There was a trend towards an association with tezosentan and other hemodynamic variables tested. However, these did not reach statistical significance when between-group comparisons were made. Tezosentan was associated with a plethora of adverse events, with an incidence of 62% and 63.6% being observed in tezosentan and placebo recipients, respectively. There were no reports of a rebound effect (*i.e.*, apparent worsening of heart failure status) in any of the patients. There were no reported episodes of hypotension or tachycardia that required treatment discontinuation in this study (31-33). The results of this study and some that follow are summarized in Table II.

The hemodynamic effects of tezosentan were similarly tested in a multicenter study in patients with advanced heart failure. A total of 38 patients (34 males and 3 females) with stable chronic heart failure (classified as NYHA class III, with CI = 2.7 l/min/m^2 and pulmonary capillary wedge pressure [PCWP] = 15 mmHg for at least 3 months) were randomized to receive placebo or tezosentan administered as 1-h i.v. infusions of increasing doses of 5, 20, 50 and 100 mg/h over 4 h. All patients received standard therapy throughout the course of the study, which could consist of an ACE inhibitor, angiotensin II receptor antagonist or diuretic. The mean age at study onset was 57 years and 97% of patients included in this analysis were Caucasian. Hemodynamic variables were evaluated during and up to 4 h postinfusion. Cardiac power, a measure of cardiac contractility, was calculated by multiplying mean arterial pressure (MAP) with cardiac output (CO). Systemic vascular resistance (SVR) was taken to be MAP % CO. CI and wedge pressure were also used as primary outcome measures in this analysis. Results from this study demonstrated a dose-dependent relationship between tezosentan administration and cardiac power when compared with placebo (22% *vs.* 4%). CI increased by 34% and 7% in active treatment and placebo recipients, respectively. SVR was also decreased; however, changes in MAP did not show statistical significance. There was also a dose-dependent decrease in wedge pressure associated with tezosentan administration. Therefore, acute administration of tezosentan was associated with an increase in cardiac

Table II: Clinical studies of tezosentan (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Congestive heart failure	Randomized	Tezosentan, 5 mg/h iv over 6 h Tezosentan, 20 mg/h iv over 6 h Tezosentan, 50 mg/h iv over 6 h Tezosentan, 100 mg/h iv over 6 h Placebo	57	Tezosentan was safe, well tolerated and effective in improving the hemodynamic profile and cardiac index in patients with moderate to severe heart failure	32, 33
Congestive heart failure	Double-blind, randomized	Tezosentan, 5 mg/h iv over 1 h → 20 mg/h iv over 1 h → 50 mg/h iv over 1 h → 100 mg/h iv over 1 h Placebo	38	Intravenous tezosentan resulted in a dose-dependent improvement in hemodynamics by increasing the cardiac index and decreasing the pulmonary and systemic vascular resistance in patients with congestive heart failure. No hemodynamic rebound was observed	34, 37
Severe renal impairment	Open	Tezosentan, 100 mg/h iv over 1 h	16	Tezosentan's pharmacokinetics and tolerability were not affected by severe renal impairment and, therefore, no dose adjustment is necessary in patients with renal impairment	38
Congestive heart failure	Double-blind	Tezosentan, 20 mg/h iv over 48 h Tezosentan, 50 mg/h iv over 48 h Dobutamine, 5 μg/kg/min over 48 h	14	Tezosentan 20-50 mg/h over 48 h was safe, well tolerated and effective in improving cardiac index, pulmonary capillary wedge pressure and systolic and diastolic pulmonary artery pressure in patients with congestive heart failure	39
Heart failure	Double-blind, randomized	Tezosentan, 50 mg/h over 24 h Tezosentan, 100 mg/h over 24 h Placebo	285	Tezosentan had dose-dependent beneficial effects on hemodynamics in patients with acute heart failure by improving cardiac index and decreasing pulmonary capillary wedge pressure, although a dose-related adverse event profile was also observed, especially hypotension. Therefore, tezosentan 50 mg/h is the optimal regimen	40
Heart failure, dyspnea	Double-blind, randomized	RITZ-1 study (n=675): Tezosentan, 50 mg/h iv over 24-72 h Placebo RITZ-2 study (n=292): Tezosentan, 50-100 mg/h iv over 1 h Placebo	967	Tezosentan appeared not to induce improvement in subjective dyspnea in the RITZ-1 study although results from the RITZ-2 study showed a significant increase in cardiac index and decrease in pulmonary capillary wedge pressure, as well as an improvement in dyspnea in patients with acute decompensated heart failure	41
Heart failure, acute coronary syndrome	Double-blind, randomized	Tezosentan, 25 mg/h i.v. over 1 h → 50 mg/h over 23-47 h Placebo	193	In the RITZ-4 study, tezosentan 50 mg did not exhibit proischemic effects in patients with acute decompensated heart failure and acute coronary syndrome, although no significant improvement in the primary composite end-point was observed and an increase in number of adverse events was reported in the treatment group	42-44
Congestive heart failure, pulmonary edema	Double-blind	Tezosentan, 50 mg/h over 15-30 min → 50-100 mg/h over 24h + standard therapy Placebo + Standard therapy	84	Tezosentan did not have any effect on the outcome of pulmonary edema in patients with exacerbation of congestive heart failure as no improvement on SO_2 was observed after 1 h of infusion	45

contractility, while inducing a decrease in wedge pressure. Tezosentan 20-50 mg/h was identified as being the optimal dose range for inducing these hemodynamic effects. No alteration in heart rate or evidence of arrhythmia was noted in these high-risk patients (34-37).

The pharmacokinetics of tezosentan were also evaluated in an open study in patients with severe renal impairment. A group of 8 patients were administered tezosentan 100 mg/h as a 1-h infusion. The volume of distribution and clearance did not vary between renal patients and the 8 healthy controls. Tezosentan produced a decrease in blood pressure and was well tolerated. The results suggested that tezosentan could be administered safely in patients with renal impairment with no need for dose adjustments (38).

Longer-term studies were carried out to confirm the positive results from short-term trials. A total of 14 patients with advanced heart failure (defined as patients with a diagnosis of NYHA class III and IV due to ischemic or dilated cardiomyopathy) were randomized to receive a prolonged 48-h infusion of tezosentan 20 mg/h, tezosentan 50 mg/h or dobutamine 5 μg/kg/min. All patients continued with other background heart failure therapies throughout the study period.Tezosentan was shown to be both effective and well tolerated in this trial. Hemodynamic improvements were exhibited although there were significant increases in both CI and stroke volume values compared with baseline. PCWP, RAP and systolic PAP values were decreased in all treatment groups. The difference from baseline in diastolic PAP did not reach statistical significance, however. As there were a small number of patients taking part in this study, it was not sufficiently powered to detect dose-related changes. Headache was the most commonly reported adverse event which occurred in 11 of the 14 patients. Hypotension, nausea and vomiting were also experienced by both tezosentan and dobutamine recipients. Heart rate was not affected by tezosentan administration, consistent with the findings from previous studies. Two tezosentan 20 mg/h patients showed evidence of atrial enlargement on ECG. There were no deaths recorded throughout the study (39).

The hemodynamic and clinical effects of tezosentan were assessed in patients with acute decompensated heart failure in need of emergency treatment. A total of 285 patients presenting to hospital with acute heart failure were included in this multicenter, randomized, double-blind, placebo-controlled trial. Male and female patients were 18 years of age and older (mean 61) at study onset, and had heart failure due to ischemic or nonischemic causes. Patient characteristics were shown to be comparable at baseline between-groups. Patients were randomized to receive a 24-h i.v. infusion of tezosentan 50 or 100 mg/h or placebo. All tezosentan doses were uptitrated from 25 mg/h in the first hour of treatment. Standard heart failure therapy was unrestricted prior to study onset, but was restricted 2 h prior to tezosentan administration. Only patients who continued to deteriorate were allowed to receive other treatment following initiation of the study drug. The primary outcome measure in this study was change in CI from baseline to 6 h. Other hemodynamic variables assessed were cardiac output (CO), pulmonary artery pressure (PAP), PCWP, and right arterial pressure (RAP). Heart rate and vascular resistance were also assessed. Clinical symptoms measured included worsening heart failure, time to death and presence of dyspnea. Worsening heart failure and time to death were recorded by attending clinicians. Patients were asked to self-assess their levels of dyspnea on a 7-point scale from 1 (markedly improved) to 7 (markedly worsened). An 8th score was given if the patient died during the course of assessment. Vital signs, full blood count and ECG measures were made at the start and end of the tezosentan infusion (40).

Results from this study showed that while tezosentan is effective in ameliorating cardiovascular symptoms associated with acute heart failure, its administration could potentially be related to a worsening renal function. This incidental finding obviously has huge implications for the use of this drug and therefore needs to be assessed in much greater detail before implications can be drawn. Hemodynamic status was significantly improved following both tezosentan 50 and 100 mg/h infusions. CI was significantly increased in both tezosentan-treated groups when compared with placebo at 6 h (0.42 *vs.* 0.41 *vs.* 0.04 in tezosentan 50 mg/h, tezosentan 100 mg/h and placebo recipients, respectively). The maximum effect of tezosentan was obtained within 4 h of infusion, with 75% of the effect being observed after only 1 h. Treatment effects were sustained for up to 6 h postinfusion. PCWP, PAP and RAP were significantly improved in tezosentan recipients, as were measures of pulmonary and systemic vascular resistance. There were no significant differences in effectiveness between tezosentan 50 and 100 mg/h in all hemodynamic parameters tested. It was suggested that tezosentan may have already reached its plateau and could therefore be as effective at 25 mg/h. Pooled analysis of patient's self-assessment of dyspnea was improved 24 h postinfusion when compared with placebo, and worsening heart failure and time to death results were comparable between groups (40).

Tolerability analysis showed that adverse events were increased in both tezosentan-treated groups compared with placebo. The most commonly occurring side effects were headache and hypotension. Hypotension was the most common cause of treatment discontinuation. There was also a trend towards a dose-response relationship between tezosentan administration and the incidence of nausea and vomiting. Renal failure was shown to be related to tezosentan administration in the context of this study. The incidence of renal failure was increased in tezosentan recipients within 48 h of treatment initiation. Tezosentan administration also seemed to be related to an increase in serum creatinine levels. Most of the patients who experienced these symptoms had a history of chronic renal failure prior to study onset. Investigators indicated that tezosentan may play some role in unmasking the potential for renal failure that already exists prior

to treatment. In this way, tezosentan was associated with an earlier presentation of renal failure but was not associated with an increased incidence of death due to renal failure. As the study was not designed to assess this apparent effect, it was not powered to be able to make proper sense of the data. Therefore, a larger scale trial with sufficient power is needed to follow up the issues discussed here (40).

The RITZ studies

The Randomized Intravenous TeZosentan (RITZ) studies are a group of placebo-controlled, multicentere, phase III clinical programs set up to test the efficacy and tolerability of tezosentan in a number of different settings. Each trial was designed to observe the effects of tezosentan in a different patient population. The RITZ studies assessed the efficacy and tolerability of tezosentan in patients with (RITZ-4) and without (RITZ-1 and 2) acute coronary syndrome. The RITZ-3 study was designed, but not commenced. The RITZ-5 study assessed the effects of tezosentan in patients with acute cardiogenic pulmonary edema.

The first two RITZ studies were designed together, with the RITZ-1 assessing the clinical effectiveness of tezosentan and the RITZ-2 assessing its effectiveness in terms of hemodynamic plus clinical changes. The RITZ-2 study assessed the hemodynamic effects of tezosentan in 292 patients with acute heart failure (defined as CI = 2.5 l/min^2, PCWP = 15 mmHg, with a need for i.v. therapy). Patients were over 18 years of age (mean 72) years at study onset and had to require hospitalization for the i.v. treatment of acute heart failure in order to be included in the analysis. Patients were randomized to receive placebo, tezosentan 50 mg/h or tezosentan 100 mg/h for 24 h. All patients remained on their standard heart failure therapy throughout the study. Concomitant medications could include i.v. vasodilators, inotropic drugs and sympathomimetic agents. Drug administration 2 h prior to study onset was maintained throughout the study, except for in the case of cardiovascular deterioration. The primary outcome variable in the RITZ-2 was change from baseline in CI at 6 h postinfusion. Results from the RITZ-2 trial were the first of the RITZ studies to be publicly published. They showed that tezosentan was effective in increasing CI in both active treatment groups compared with placebo (treatment effect of 38% and 37% in tezosentan 50 and 100 mg/h groups, respectively). PCWP was significantly decreased in both tezosentan groups compared with placebo. Tezosentan administration was further associated with a statistically significant amelioration of clinical signs (*i.e.*, fewer tezosentan-treated patients experienced dyspnea when compared with placebo-treated patients) (41).

The RITZ-1 study assessed the clinical efficacy of tezosentan 50 mg/h *versus* placebo in 675 noncatheterized patients with acute heart failure. The main outcome assessed in the RITZ-1 study was presence of dyspnea (in the absence of other hemodynamic markers). Results from the RITZ-1 trial were in contrast to the previously reported results from the RITZ-2. While the RITZ-2 showed tezosentan to be significantly associated with favorable hemodynamic changes, the RITZ-1 results did not meet their primary objective of improving the dyspnea associated with heart failure. Secondary clinical endpoints such as worsening heart failure and time to death also did not reach statistical significance in this analysis. Investigators remarked that this disparity in findings underlines the problems that researchers face when establishing the difference between clinical and biochemical measures of efficacy. Until the RITZ-1 was conducted, most of the trials had assessed hemodynamics as opposed to clinical variables as their primary outcome measure. Therefore, what may be a significant difference in hematological status may not mean that any clinical benefit is actually incurred. These discrepancies need to be evaluated in further trials (41).

The RITZ-4 study assessed the clinical outcome of tezosentan in patients with acute heart failure complicated by acute coronary syndrome. The RITZ-4 was the first study to investigate this high-risk patient population specifically, in spite of the fact that ischemia is a major etiological factor in the manifestation of heart failure. Acute coronary syndrome was defined as the presence of ischemic symptoms, a new Q-wave, presence of S-T-elevation or depression > 1 cm, T-wave inversion or positive cardiac enzymes for the purposes of this study. A total of 193 patients with both heart failure and coronary syndrome were randomized to receive placebo (n=96) or intravenous tezosentan 50 mg/h (n=97) for 24-48 h following a double-blind trial design. The tezosentan dose was uptitrated from 25 mg/h in the first hour of treatment. All patients received their normal background heart failure therapy throughout the study. Intravenous diuretics were not given 2 h previous to or 6 h following tezosentan. The primary clinical outcome variables of the RITZ-4 were worsening heart failure (defined as initiation or increase of background therapies with ventilatory or circulatory support), ischemia, myocardial infarction (MI) or death within 72 h of drug administration. Results of the RITZ-4 showed tezosentan to be ineffective in this patient population, with no significant differences between active treatment and placebo recipients being observed. The combined incidence of worsening heart failure, ischemia, MI and death within 72 h was 24.2% and 28.9% in placebo and tezosentan recipients respectively. As there were relatively few patients in this trial, it could be that the study was insufficiently powered to detect differences here. There was no evidence of a proischemic effect in the absence of treatment benefit, however. Paradoxically, tezosentan recipients were shown to have a higher incidence of worsening heart failure when compared with placebo recipients, although this trend did not reach significance (19.6% *vs.* 11.6%). Survival rates were comparable at 6 months (42-44) (Fig. 2).

Adverse events monitoring revealed that tezosentan was less favorable than placebo, with 81.1% and 91.8%

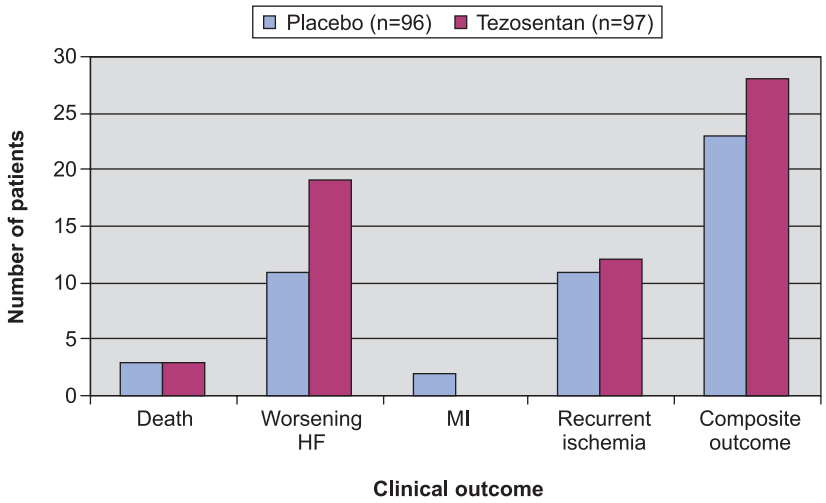


Fig. 2. Clinical outcome variables from the RITZ-4 study (refs. 42-44).

of placebo and recipients reporting at least 1 adverse event, respectively. Most problems arose due to the increased incidence of symptomatic hypotension, resulting in the withdrawal of 7 placebo recipients and 17 tezosentan recipients from the study. Headache and renal insufficiency were also associated with tezosentan dosing. Incidence of renal failure was found to be 7.2% and 2.1% in the tezosentan-treated and placebo-treated groups, respectively. The authors suggested that such effects may be secondary to the induction of a hypotensive state rather than a nephrotoxic drug effect per se. It is possible that vasodilatory effects could result in a decreased filtration pressure, leading to the development of renal failure. The increased prevalence of side effects in the absence of clinical benefit indicated that the dosing schedule was too high. Therefore, the effectiveness of tezosentan may be improved following a different dosing regimen. If the renal insufficiency and worsening heart failure are a consequence of hypotension rather than a nephrotoxic effect, then reducing the dose of tezosentan could potentially reduce these side effects. Further studies are, in fact, currently under way to assess the hemodynamic and clinical effects of tezosentan at lower doses (42-44) (Fig. 3).

The RITZ-5 study was a phase III multicenter, randomized, controlled trial designed to estimate the addition of i.v. tezosentan to standard therapy in patients with acute cardiogenic pulmonary edema. As tezosentan is effective in treating symptoms of heart failure, investigators elected to identify its effects on pulmonary edema. Pulmonary edema was in this context defined as the decreased oxygen saturation and respiratory failure

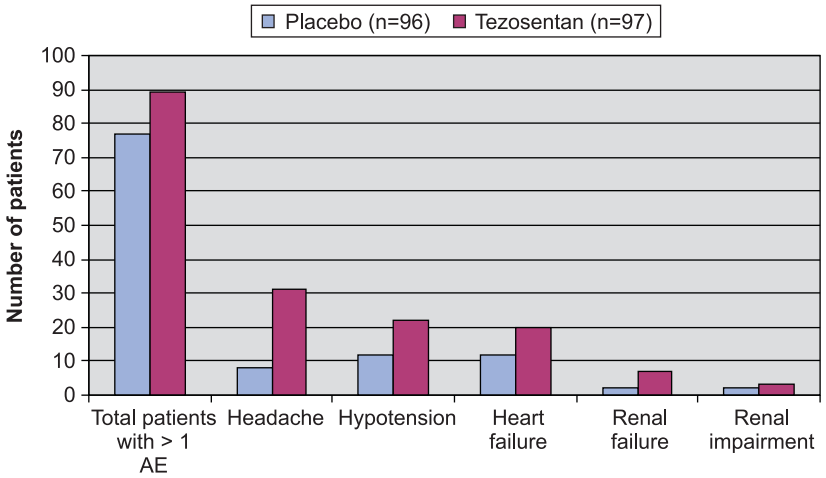


Fig. 3. Adverse events from the RITZ-4 study (refs. 42-44).

associated with acute heart failure. This was the first trial conducted to analyze the efficacy of tezosentan in this context. A total of 84 male and female patients with pulmonary edema secondary to acute heart failure were randomized to receive placebo or i.v. tezosentan 50 mg/h for 15-30 min, followed by 50-100 mg/h for up to 24 h. All patients received standard therapy, which could consist of a combination of O_2, furosemide, isosorbide dinitrate and morphine. Pulmonary edema was defined as an O_2 saturation (SO_2) of less than 90% in spite of O_2 8 l/min treatment. The primary outcome measure in the RITZ-5 trial was change in arterial SO_2 at 1 h. Rate of refractory pulmonary edema, myocardial infarction and death were assessed as secondary variables. Increase in the use of other heart failure medications was also calculated (45).

Results showed that tezosentan was comparable to placebo in its ability to improve SO_2, with tezosentan and placebo recipients exhibiting an increase in SO_2 of 7.6 and 9.1 units at 1 h, respectively. As this was the primary outcome variable, investigators did not continue to assess the effectiveness of tezosentan on the secondary variables. Ad hoc analysis showed that baseline SO_2, mean arterial pressure and ejection fraction values were predictive of treatment failure.

Tezosentan was associated with an increased risk of hypotension (38% of active treatment recipients compared with 19% of placebo recipients, respectively). Interestingly, tezosentan was not associated with an increase in the incidence of renal failure in this study. There was, however, a significant difference in serum creatinine levels between groups (19 *vs.* 3 μmol/l). Investigators commented that while the role of endothelin is well established in the realm of heart failure, its association with pulmonary edema is ill defined (45).

Results from the RITZ trials showed that while tezosentan has been associated often with benefits to hemodynamic status, this does not necessarily reflect a clinical benefit to the patient. Moreover, tezosentan could potentially be producing a deleterious effect in patients at the doses studied. Therefore, in all trials being conducted from now on, clinical markers of efficacy as well as morbidity and mortality endpoints have become of primary importance (46). Unsatisfactory results from the RITZ studies led to the development of a new clinical program where tezosentan will be tested at lower doses than originally tested. It is thought that these lower doses will bring about hemodynamic changes without the associated side effects of the higher doses studied in the RITZ trials. Investigators still believe that tezosentan has potential benefit for the treatment of heart failure and are proceeding with a phase III registration study. The Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS) was initiated in April 2003. This randomized, double-blind, placebo-controlled study was designed in the light of results gained from the RITZ trials. It will set out to evaluate morbidity and mortality outcomes following tezosentan administration. A total of 1,800 patients are expected to take part in this investigation, with study results anticipated in 2005. Investigators are planning an interim analysis in 2004 to ensure that the benefits of tezosentan are indeed outweighing the possible adverse associations. It is thought that the results of this trial may confirm tezosentan's effectiveness in the treatment of acute heart failure. Also, it is hoped that a more optimal tezosentan dose may be identified. Tezosentan is also being assessed in patients with hepatorenal syndrome (*i.e.*, patients with liver cirrhosis with concurrent renal impairment). Two phase II trials are currently under way, namely the Renal Function Study and the Liver Function Study (3).

Conclusions

While preliminary studies showed tezosentan to have a highly significant positive hemodynamic effect in patients with heart failure, more recent results have shown that tezosentan does not improve survival or reduce the frequency of worsening heart failure, yet is associated with a higher incidence of renal failure. Therefore, despite theorized benefit of this mixed ET receptor antagonist, no clinical benefits were established. It must be remembered, however, that negative results from one clinical program does not necessarily mean that the drug is not effective. Moreover, careful analysis must now be undertaken in order to properly establish the efficacy and tolerability of tezosentan within this context. Disappointing results have led to further studies with tezosentan but at lower doses of the compound than initially tested. A 2-year phase III study is currently under way to evaluate morbidity and mortality in patients with heart failure. As well as this, comparative trials between tezosentan and standard therapies for heart failure will need to be conducted before any conclusive statements can be made.

Source

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