MINIREVIEW

Clinical Trials of Endothelin Antagonists in Heart Failure: A Question of Dose?

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Circulating plasma endothelin (ET)-1 concentrations are substantially elevated, and correlate with the hemodynamic severity and New York Heart Association (NYHA) class, in patients with chronic heart failure (CHF). In early preclinical studies involving different models of experimental heart failure, ET antagonists reduced cardiac pressures, increased cardiac output, and prolonged survival. ET receptor antagonists also impressively improved systemic and pulmonary hemodynamics in patients with CHF, without causing neurohormonal activation. However, recent clinical trials, including the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) and EARTH (Endothelin A Receptor Antagonist Trial in Heart Failure) studies, have shown neutral effects in terms of mortality and symptoms. This paper describes the possible reasons why benefit was not seen in these clinical studies, and suggests what lessons can be learnt from the way the studies were undertaken to apply to future studies. Exp Biol Med 231:696–699, 2006

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The Role of Endothelin in Chronic Heart Failure

Endothelin (ET)-1 binds to ET_A and ET_B receptors on vascular smooth-muscle cells, resulting in profound vasoconstriction and cellular proliferation. In contrast, activation of endothelial cell ET_B receptors releases nitric oxide and prostacyclin, which are antimitotic and mediate vasodilation. Endothelial cell ET_B receptors are also responsible for clearance of ET-1 from the circulation, and renal ET_B receptors may contribute to natriuresis (1).

Similar to several other neurohumoral systems, the ET system is activated in chronic heart failure (CHF). In initial studies using animal models of experimental heart failure, treatment with either mixed or ET_A selective antagonists significantly ameliorated left ventricular dysfunction, prevented ventricular remodeling, and prolonged survival after coronary artery ligation (2). Selective ET_B antagonists, however, increased pulmonary and diastolic pressures and reduced cardiac output (3).

Plasma ET-1 concentrations in patients with CHF are correlated with both morbidity and mortality, prompting investigators to pursue the therapeutic potential of ET blockade in CHF (2). Investigators have examined the short-term hemodynamic effect of ET antagonists in patients with CHF. Two weeks of oral treatment with the mixed ET antagonist, bosentan, reduced pulmonary vascular resistance by approximately 40% and systemic vascular resistance by 30%, with no change in heart rate (4). Acute treatment with sitaxsentan, a selective ET_A blocker, however, seemed to have a preferential effect on the pulmonary circulation; acute administration resulting in significant decreases in pulmonary artery systolic pressure and pulmonary vascular resistance but no effect on systemic hemodynamics (5).

In the light of such encouraging results, clinical trials were swiftly organized. In the Research on Endothelin Antagonists in Chronic Heart Failure (REACH-1) study (6),

the long-term effects of the mixed ET antagonist, bosentan, ($n = 244$) versus placebo ($n = 126$) in patients with CHF (New York Heart Association [NYHA] Class IIIB/IV) were assessed. This trial was halted prematurely because of an increased incidence of elevated liver transaminase levels. At the time that the trial was stopped, however, patients who had been maintained on therapy during a 6-month period demonstrated a trend toward a reduced risk of heart failure–related mortality and morbidity. The possibility that long-term bosentan therapy at a lower dose would improve the clinical course of heart failure patients was evaluated in two companion large-scale clinical trials, Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure (ENABLE) 1 and 2, which were conducted in the United States and Europe, respectively. Eight hundred and five patients with NYHA Class IIIB/IV CHF administered bosentan were compared with 808 patients treated with placebo. However, the results failed to demonstrate that the addition of bosentan to standard treatment reduced either morbidity or mortality (7). Treatment of 419 patients (Class II/III CHF) randomized to another mixed antagonist, enrasentan, or placebo failed to show benefit in a composite end point, including NYHA Class, hospitalization rate, and global assessment, and, in fact, showed a trend in favor of placebo (Enrasentan Cooperative Randomized Evaluation [ENCOR] study) (8). None of these clinical trials have been fully published and subjected to external peer review. Therefore, the effects of treatment with ET antagonists in CHF have not been released into the public domain, and there has been no opportunity to look across the trials to see whether there are subpopulations that might benefit, or to examine other aspects of these studies (such as plasma ET-1 concentrations).

In the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH) study, 642 patients with NYHA Class II–IV CHF were randomized to treatment either with darusentan or placebo during 24 weeks (9). The primary end point was the change in left ventricular end systolic volume (LVESV) measured by magnetic resonance imaging. No significant difference was seen in LVESV from values after placebo treatment for any dose of darusentan. Furthermore, there were no differences seen in terms of mortality or the progression of heart failure. Plasma concentrations of ET-1 increased dose-dependently in all groups receiving darusentan ($P = 0.0028$).

Why Did the Clinical Trials Yield Negative Results?

The expectation of likely clinical benefit of ET antagonists in CHF, based on the results of initial preclinical and human hemodynamic studies, has clearly not been fulfilled by the results of the clinical trials. There are a number of possible explanations for this disparity.

First, although, for some drugs, such as angiotensin-converting enzyme (ACE) inhibitors, acute improvement of hemodynamic parameters in CHF patients can translate into reduced morbidity and mortality when used during a longer term in clinical trials (10), this relationship does not stand for all therapeutic agents. For example, treatment with inotropic agents improves the cardiac index of CHF patients when given acutely, but long-term administration to patients with advanced CHF increases mortality (11). The same may hold for ET antagonists; although they clearly improve cardiac output acutely, all clinical trials to date indicate that ET antagonists do not reduce morbidity or increase survival with long-term administration.

Second, although early studies using ET antagonists demonstrated improvements in hemodynamic variables and mortality in animal models of CHF after myocardial infarction (12, 13), thought to be caused by their action on cardiac remodeling, a recent meta-analysis of numerous preclinical studies has shown that ET antagonists have no net beneficial effect on mortality (14). It has been demonstrated that the early administration of ET antagonists after myocardial infarction resulted in increased mortality, most likely because of a remodeling-related increase in cardiac dimensions (15, 16).

Third, ET blockade might have been successful in the treatment of CHF if it had been introduced before the use of ACE inhibitors, β-blockers, and spironolactone, which are now established as standard CHF therapies. Once two neurohumoral systems are blocked, inhibition of a third system may provide little additional benefit, or the benefit may not be sufficient to be observed in the relatively small clinical trials performed to date. Nevertheless, it seems unlikely that such small benefits, in the global population of patients with NYHA III/IV CHF, will be clinically meaningful or cost-effective.

Fourth, there may be specific patient groups within the total population of CHF patients in which ET blockade is beneficial. ET antagonists are known to reduce pulmonary artery pressures in both patients with primary pulmonary hypertension and secondary pulmonary hypertension caused by left ventricular dysfunction (17, 18). Perhaps, if only CHF patients with raised pulmonary arterial pressures had been included, a clear benefit of treatment with ET antagonists would have emerged.

Finally, the benefits of ET blockade in CHF may derive from a truly ET_A-selective approach. In CHF patients, ET_A-selective antagonism, with BQ-123, reduced systemic vascular resistance and increased cardiac output compared with mixed ET blockade (18). In such patients, selective blockade of ET_B, with BQ-788, had such a deleterious effect, causing systemic vasoconstriction and elevation of plasma ET-1 concentrations (19), that the authors withdrew this part of the study. In patients with chronic renal failure and hypertension, selective ET_A blockade with BQ-123 reduced renal vascular resistance and increased natriuresis, effects not seen with mixed ET_A and ET_B receptor antagonism (20). Hence, selective ET_A receptor antagonism might be more likely than the $ET_{A/B}$ blocking approach to

avoid fluid retention in CHF patients. In the coronary microcirculation of patients with ischemic heart disease, endothelial dysfunction, a known independent risk factor for the development of cardiovascular disease (21), was improved after ET_A, but not combined $ET_{A/B}$, blockade (22).

All of the ET antagonists currently under clinical development are relatively ET_A selective (Table 1). However, they are arbitrarily classified as ET_A receptor antagonists if they demonstrate a more than 100-fold selectivity for the ET_A over the ET_B receptor (23). Both genetic knockout (24) and pharmacologic blockade of the ET_B receptor in animals (25) and humans (26) results in elevated plasma ET-1 concentrations because of impaired clearance of ET-1. Administration of very high doses of relatively ET_A-selective agents can result in ET_B receptor blockade (27), causing increased ET-1 plasma concentrations. In contrast, there is no significant increase in ET-1 plasma concentrations after either acute ET_A blockade with a range of doses of BQ-123 (19, 26, 28) or chronic ET_A antagonism with ZD-4054 during 14 days (29). Raised plasma ET-1 concentrations, in the presence of an endothelin antagonist, can, therefore, be used as an index of ET_B receptor binding by that drug.

The first three clinical trials of ET antagonists in CHF (REACH, ENABLE, and ENCOR) have not been published, therefore, their detailed results, including the effect of drug treatment on plasma ET-1 concentration, are not in the public domain. However, treatment with darusentan, the most ET_A selective of the agents studied in CHF patients, resulted in a dose-dependent increase in plasma ET-1 concentrations in the EARTH study (9). Thus, we can conclude that the doses of ET antagonist used in this, and very likely in the other trials, did not offer truly ET_A selective blockade.

What Can Be Learned from the ET Antagonists in CHF Clinical Trials?

Of the clinical trials of ET antagonists in CHF, only the EARTH study has been published. Until the data from all of the clinical trials in CHF are made publicly available, full independent analysis and interpretation of the results, from which patients might serve to benefit, will not be possible.

Although the EARTH study investigated the effect of an agent with modest selectivity for the ET_A receptor in CHF, at the doses used in this trial it seems to have had significant activity at the ET_B receptor. Truly ET_A-selective ET antagonism, therefore, remains untested in these patients, although, sadly, reduced interest from the pharmaceutical industry in this area means that such a trial is unlikely to be organized in the near future.

Even if the consensus is that ET antagonists do not confer benefit in CHF, they are now licensed for the treatment of pulmonary hypertension and are being developed for other clinical applications in chronic renal disease, oncology, and the management of pain (30). We hope that valuable lessons, in terms of efficacy, toxicity, dosing, and receptor selectivity, can be learned and applied to these new clinical applications for ET antagonists.

Table 1. The Names, Drug Codes, and Selectivity for the ET_A Receptor for a Range of ET Antagonists Used in Preclinical and Clinical Studies

ET antagonists		
Drug code	Drug name	ET_A selectivity
J-104132	N/A	×5
RO-470203	Bosentan	×20
RO-610612	Tezosentan	×30
SB-217242	Enrasentan	×110
LU-135252	Darusentan	×130
A-627; A-127722	Atrasentan	×1860
BQ-123	N/A	×2500
TBC-11251	Sitaxsentan	×6500
ZD-4054	N/A	>×10,000

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