CARDIOVASCULAR MEDICINE

Comparison of the dual receptor endothelin antagonist enrasentan with enalapril in asymptomatic left ventricular systolic dysfunction: a cardiovascular magnetic resonance study

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Objective: To compare the effect of the dual endothelin A/B receptor antagonist enrasentan with enalapril on left ventricular (LV) remodelling.

Methods: Multicentre, randomised, double blind, parallel group study of 72 asymptomatic patients with LV dysfunction. Patients received enrasentan (60–90 mg/day) or enalapril (10–20 mg/day). The primary end point was the change in LV end diastolic volume index (EDVI) after six months' treatment.

Results: LV EDVI increased with enrasentan but decreased with enalapril ($3.9 (1.8) v -3.4 (1.4) \text{ ml/m}^2$, $p = 0.001$). Enrasentan increased resting cardiac index compared with enalapril ($0.11 (0.07) v -0.10 (0.07) \text{ l/m}^2$, $p = 0.04$), as well as LV mass index ($0.67 (1.6) v -3.6 (1.6) \text{ g/m}^2$, $p = 0.04$). Other variables were comparable between groups. Enalapril lowered brain natriuretic peptide more than enrasentan ($-19.3 (9.4) v -5.8 (6.9) \text{ pg/ml}$, $p = 0.005$). Noradrenaline (norepinephrine) ($p = 0.02$) increased more with enrasentan than with enalapril. Enrasentan was associated with more serious adverse events compared with enalapril (six (16.7%) patients v one (2.8%), $p = 0.02$); the rate of progression of heart failure did not differ.

Conclusion: In asymptomatic patients with LV dysfunction, LV EDVI increased over six months with enrasentan compared with enalapril treatment, with adverse neurohormonal effects. This suggests that enrasentan at a dose of 60–90 mg/day over six months causes adverse ventricular remodelling despite an increase in the resting cardiac index.

Heart failure (HF) is characterised by progressive deterioration in cardiac function and symptoms resulting in high morbidity and mortality. Patients with asymptomatic left ventricular (LV) systolic dysfunction are at high risk of HF and death even when ejection fraction (EF) is only mildly impaired. Neurohormone activation, linked to adverse ventricular remodelling, may be an important pathway for progression. The importance of the renin-angiotensin-aldosterone and sympathetic nervous systems is well documented, but more recently the endothelins have also been linked with disease progression.

Endothelin 1 is a 21 amino acid vasoactive peptide that is released predominantly from vascular endothelium¹ and is synthesised by a variety of cell types including vascular smooth muscle, cardiomyocytes, and cardiac fibroblasts.² It is the predominant isoform of the endothelin peptide family and mediates both autocrine and paracrine actions through two G protein coupled receptor subtypes (endothelins A and B). Endothelin stimulates potent vasoconstriction and cell proliferation through activation of endothelin A receptors on vascular smooth muscle cells, whereas endothelin B receptors are primarily involved in the mediation of vasodilatation through effects on the clearance of endothelin, inhibition of endothelial apoptosis, release of nitric oxide and prostacyclin, and inhibition of endothelin converting enzyme 1 expression.³ Local activation of the endothelin system has been documented in hypertension, atherosclerosis, and HF. Endothelin augments sympathetic activity, enhances the activity of the renin-angiotensin-aldosterone system with modulation of sodium reabsorption,⁴ mediates cardiac

hypertrophy through upregulation of GATA4 DNA,⁵ and induces myocyte injury.

In animal models of chronic HF, endothelin receptor antagonists have mostly shown significant promise with improved survival, reduced preload and afterload, and decreased LV hypertrophy, dilatation, and cardiac fibrosis.⁶ The combined endothelin A/B receptor antagonist bosentan has been evaluated in patients with HF, including those treated with angiotensin converting enzyme (ACE) inhibitor, showing haemodynamic improvements with reduced peripheral and pulmonary vascular resistance and increased cardiac output.³ A direct relation was observed between endothelin concentrations and bosentan effect in the patients. Enrasentan is an orally active mixed endothelin A/B receptor antagonist with a 100-fold greater affinity for the endothelin A receptor. It is effective in animal models of cardiovascular disease including hypertension and HF. Enrasentan treated rats with cardiac hypertrophy and dysfunction induced by banding had higher stroke volume and cardiac index, improved survival, and reduced LV mass index, aldosterone, and pro-atrial natriuretic peptide concentrations.⁷ The

Abbreviations: ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; CARMEN, carvedilol ACE inhibitor remodelling mild CHF evaluation; CMR, cardiovascular magnetic resonance; EARTH, endothelin A receptor antagonist trial in heart failure trial; EDVI, end diastolic volume index; EF, ejection fraction; ENABLE, endothelin antagonist bosentan for lowering events; ENCOR, enrasentan cooperative randomised evaluation; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association; REACH-1, randomised endothelin antagonism in chronic heart failure with bosentan

present study is the first to have compared an endothelin antagonist, enrasentan, directly with an ACE inhibitor, enalapril, in asymptomatic patients with LV dysfunction. The goal was to determine whether treatment with an endothelin receptor antagonist may have an early role in slowing the progression of HF.

METHODS

Study design

We performed a phase II, multicentre, double blind, parallel group study, in which asymptomatic patients with LV systolic dysfunction (New York Heart Association (NYHA) class I) were randomly assigned to receive enrasentan or enalapril once daily. Although long term ACE inhibitors have been shown to be beneficial, these patients have a low morbidity and mortality over the short term, and it was considered a direct comparison over six months of two active agents and intensive monitoring would not compromise patient safety. Consecutive patients meeting the inclusion criteria were recruited from cardiology outpatient clinics; the majority of patients (70%) were being followed up for documented previous myocardial infarction. The remainder of patients were being followed up for hyperlipidaemia (12%), atypical chest pain (8%), and mild valve disease (10%). Enrasentan was initiated at 30 mg and enalapril at 2.5 mg, both once daily. Dosage was uptitrated over 6–10 weeks to reach a maximum tolerated level with a minimum dose of 60 mg of enrasentan or 10 mg of enalapril, and a maximum dose of 90 mg of enrasentan or 20 mg of enalapril. Patients remained in the maintenance phase for six months at this dose and then continued into a follow up period of up to 10 days.

LV dysfunction was defined as an EF during screening of $\leq 40\%$ measured by two dimensional echocardiography. Experienced operators performed the studies by using fundamental frequency with the subject in the left lateral recumbent position in breath hold expiration. Subsequently all echocardiographic studies were analysed in a central core laboratory.

Exclusion criteria were acute coronary syndromes within six weeks, clinically significant valve disease, hypertrophic cardiomyopathy, uncontrollable or symptomatic arrhythmias, systolic blood pressure < 85 mm Hg or > 160 mm Hg, second or third degree heart block, significant co-morbidity, and any contraindications to cardiovascular magnetic resonance (CMR) imaging. Patients were not allowed to enter the study if they had received HF treatment in the preceding six weeks or were concomitantly taking for other reasons ACE inhibitors or angiotensin receptor blockers. Patients taking short acting calcium channel blockers or β blockers were admissible only if they had been taking a stable dose without adjustment for greater than three months. Treatment with diuretics was not permitted before entry into the study, but these could be prescribed during the study if required to control developing symptoms of HF. Doses of other concomitant medications could be altered if necessary, at the discretion of the investigator, throughout the study. The study protocol was approved by the institutional ethics review committee at each study site, and all patients provided written informed consent before entry into the study. Patients were recruited from three centres in the UK. A single computer generated randomisation code was used for all sites and was coordinated by an independent randomisation centre. Both the investigator and patient were blinded to all study medication. Enrasentan was provided by SmithKline Beecham. Matching capsules containing enalapril were manufactured by Merck.

Study objectives

The primary study objective was to compare the effects of enrasentan with those of enalapril on LV end diastolic

volume index (EDVI). The secondary objectives were to compare the drug effects on other remodelling and cardiac function measurements, circulating neurohormones, the safety of enrasentan, progression of HF, and patient symptoms.

Cardiovascular magnetic resonance imaging

CMR cardiac volume and function scans were recorded at baseline and at six months by using standard techniques.⁸ The CMR scans were read in a core laboratory at Royal Brompton Hospital and analysed with dedicated software (CMRtools, Imperial College, London, UK).

Laboratory analyses

Blood was obtained at baseline and after completion of the study at six months, or at early withdrawal, for brain natriuretic peptide (BNP) and noradrenaline (norepinephrine) concentrations. Plasma samples for neurohormonal concentrations were obtained at all visits with 10 ml EDTA syringes used for sampling. Plasma was separated and stored at -80°C until assays were performed. Frozen plasma samples were forwarded to a central laboratory for processing. BNP was measured with an immunoradiometric assay (Shionogi; Osaka, Japan). The intra-assay and interassay coefficients of variation were 3.9% and 4.8%, respectively, with a lower detection limit of 1 pg/ml (0.6 pmol/l). Endothelin concentrations were assessed once only during the screening phase. Endothelin concentrations were measured by enzyme immunoassay and noradrenaline concentrations were measured by high performance liquid chromatography. Clinical laboratory safety tests were taken in the screening phase, during the uptitration period, and at one, three, and six months of the maintenance phase or at early withdrawal.

Progression of HF

HF progression was defined by any of the following: requirement for addition of a diuretic, worsening of NYHA class, hospitalisation for HF, or death.

Clinical HF self assessment

Clinical HF was determined at one, three, and six months during the maintenance phase of the study or at early withdrawal. The patient was asked to answer the question "How do you feel today as compared with how you felt before taking this medication?" The patient rated global clinical status on a seven category scale (greatly improved, moderately improved, mildly improved, no change, slightly worse,

Table 1 Baseline demographic characteristics of the study patients randomly assigned to enrasentan or enalapril treatment

Characteristic	Enrasentan (n = 36)	Enalapril (n = 36)	p Value
Men	35 (97%)	31 (86%)	0.07
White	33 (92%)	34 (94%)	0.6
Age (years)			
≤ 65	22	19	0.5
65–74	13	16	0.5
≥ 75	1	1	0.8
Mean (SEM)	61.4 (1.5)	62.6 (1.4)	0.6
Range	35–76	41–77	
Weight (kg)			
Mean (SEM)	83.3 (2.8)	75.9 (2.2)	0.01
Range	59–121	53–102	
Height (cm)			
Mean (SEM)	173 (1.4)	169 (1.3)	0.008
Range	151–187	150–185	

Table 2 Baseline cardiovascular conditions and medications of the study patients

Baseline conditions	Enrasentan (n = 36)	Enalapril (n = 36)	p Value
Angina pectoris	12 (33%)	14 (39%)	0.6
Hypertension	6 (17%)	4 (11%)	0.5
Diabetes (non-insulin dependent)	2 (5.6%)	4 (11%)	0.4
Diabetes (insulin dependent)	0	1 (2.8%)	0.3
Prior myocardial infarction	24 (67%)	25 (69%)	0.8
CABG	25 (69%)	22 (61%)	0.45
Hyperlipidaemia	14 (39%)	13 (36%)	0.8
Conduction disorder	5 (14%)	7 (19%)	0.5
Peripheral vascular disease	3 (8.3%)	3 (8.3%)	0.7
AV block	1 (2.8%)	4 (11%)	0.2
Concurrent medications			
Aspirin	32 (89%)	33 (92%)	0.7
β Blockers	9 (25%)	11 (31%)	0.6
Statin	5 (14%)	7 (19%)	0.5

AV, atrioventricular; CABG, coronary artery bypass graft.

moderately worse, or much worse) as used in previous HF trials.⁹

Statistical methods

The study was powered at 90% with a significance level of $p = 0.05$ to detect a difference of 2.5 ml/m² in LV EDVI between enrasentan and enalapril. All remodelling data were tested by analysis of variance and values are shown as mean (1 SD), except where stated. The correlations between the plasma concentrations of neurohormones and remodelling variables were assessed by Spearman's rank correlation. The progression of HF and the clinical patient self assessments were analysed by Fisher's exact test. All safety data were analysed by using the intention to treat population, which was defined as all patients who received at least one dose of randomised medication and who had been assessed once after the baseline assessments. Comparisons were made at study end point, defined as the last available record of the randomly assigned patients while being treated.

All patients were evaluated for clinical safety and tolerability including determination of all adverse experiences and abnormal vital signs regardless of their relation to the study medication. Laboratory values and ECG changes were reported as adverse events if clinically significantly abnormal in the investigator's opinion. Non-compliant patients were included from the analysis. All tests were two sided and a value of $p \leq 0.05$ was considered significant.

RESULTS

Baseline characteristics and analysis populations

Of 96 patients enrolled into the study, 72 were randomly assigned to treatment (36 to enalapril and 36 to enrasentan) and entered the titration phase, 67 (93.1%) entered the maintenance phase, and 63 (87.5%) completed the study. Tables 1–3 show baseline characteristics of the patients. Treatment groups were comparable at baseline except for body height and weight parameters, right ventricular volumes, resting cardiac index, and BNP. Sixty four patients (95.5%) entered the maintenance phase of the study taking the maximum dose of enrasentan or enalapril. Of the 63 patients completing the full protocol, 32 patients were randomly assigned to enrasentan and 31 to enalapril. After treatment randomisation, four patients (11.1%) withdrew from the enrasentan group and five (13.9%) from the enalapril group.

Primary outcome measure

Treatment with enrasentan resulted in an increase in LV EDVI of 3.9 (1.8) ml/m² ($p = 0.04$) compared with a

Table 3 Baseline haemodynamic and neurohormone parameters of the study patients

Baseline characteristics	Enrasentan (n = 36)	Enalapril (n = 36)	p Value
Body surface area (m ²)	1.92 (0.04)	1.81 (0.04)	0.02
Sitting systolic BP (mm Hg)	132.6 (2.9)	135.9 (2.6)	0.3
Sitting diastolic BP (mm Hg)	79.0 (1.5)	80.0 (1.5)	0.5
Sitting heart rate (beats/min)	67.5 (1.7)	67.4 (2.4)	0.9
LV EDVI (ml/m ²)	65.2 (3.0)	63.5 (3.5)	0.23
LV ESVI (ml/m ²)	29.1 (2.5)	24.9 (2.6)	0.1
LV EF (%)	61 (2.0)	63 (2.0)	0.37
RV ESVI (ml/m ²)	26.1 (1.1)	21.8 (1.1)	0.005
RV EDVI (ml/m ²)	69.7 (1.7)	64.4 (2.0)	0.004
LV mass index (g/m ²)	97.6 (2.4)	94.2 (3.4)	0.17
RV mass index (g/m ²)	25.9 (0.8)	24.7 (0.7)	0.15
LV sphericity index	0.63 (0.01)	0.63 (0.02)	0.95
Cardiac index at rest (l/min/m ²)	2.37 (0.1)	2.14 (0.1)	0.03
Brain natriuretic peptide (pg/ml)	53.2 (8.23)	72.7 (18.7)	0.03
Noradrenaline (nmol/l)	2.13 (0.14)	2.26 (0.17)	0.4
Plasma endothelin (fmol/ml)	1.64 (0.46)	1.14 (0.31)	0.3

Data are mean (SEM).

BP, blood pressure; EDVI, end diastolic volume index; EF, ejection fraction; ESVI, end systolic volume index; LV, left ventricular; RV, right ventricular.

Figure 1 Comparison of change in left ventricular end diastolic volume index (LVEDVI) after six months' treatment.

reduction of -3.4 (1.4) ml/m² in the enalapril group ($p = 0.01$). The between groups difference was significant ($p = 0.001$) (fig 1).

Secondary outcome functional measures

The two treatment groups did not differ significantly in the change from baseline LV end systolic volume index or EF (table 4) but LV mass index differed significantly between groups, with a reduction with enalapril but no change with enrasentan. The change in resting cardiac index differed significantly between the groups (0.11 (0.07) v -0.10 (0.07) l/min/m², $p = 0.04$) (fig 2). The stroke volume increased

Table 4 Change from baseline in cardiac remodelling parameters after six months' treatment

Change from baseline	Enrasentan (n = 31)	Enalapril (n = 32)	p Value
LV EDVI (ml/m ²)	3.9 (1.8)	-3.4 (1.4)	0.001
LV ESVI (ml/m ²)	-0.06 (1.1)	-2.0 (0.93)	0.2
LV EF (%)	1.8 (0.8)	1.5 (1.0)	0.8
Cardiac index at rest (l/min/m ²)	0.11 (0.070)	-0.096 (0.069)	0.04
LV mass index (g/m ²)	0.67 (1.6)	-3.8 (1.6)	0.04

Data are mean (SEM).

from baseline with enrasentan (75.1 (15.5) ml to 82.9 (19.4) ml, $p = 0.002$), with a trend towards reduction with enalapril (71.7 (16.9) to 68.9 (20.2) ml, $p = 0.09$).

Over the treatment period the groups did not differ significantly in systolic blood pressure (enrasentan -4.1 (14.4) mm Hg *v* enalapril -9.3 (19.2) mm Hg, $p = 0.20$) or in diastolic blood pressure (enrasentan -5.2 (8.4) mm Hg *v* enalapril -5.4 (10.8) mm Hg, $p = 0.93$). The heart rate response to treatment did not differ (enrasentan 0.83 (10.8) *v* -3.4 (9.9) beats/min, $p = 0.29$).

A trend to reduction in haemoglobin on enrasentan was not significant and haemoglobin did not change with enalapril treatment. The change in the enalapril group from baseline to the end of the study was -9 (80) g/l ($p = 0.26$) and the change in the enrasentan group was -200 (106) g/l ($p = 0.12$). The differences between the groups were not significant.

Neurohormone measurements

Baseline BNP concentrations were raised in both groups but with a significantly higher concentration in the enalapril group (72.7 (19) *v* 53.2 (8.2) pg/ml, $p = 0.03$). Both treatments reduced BNP concentrations, although this reduction was greater in the enalapril group (-19.3 (9.4) *v* -5.8 (6.9) pg/ml, $p = 0.005$). Noradrenaline ($p = 0.02$) increased more with enrasentan than with enalapril (fig 3). Plasma endothelin concentrations at baseline were not correlated with the cardiac remodelling parameters of LV EDVI, end systolic volume index, and EF.

Progression of HF

By the predefined criteria, in the enrasentan group eight (22%) patients had a deterioration in their condition compared with 10 (28%) patients in the enalapril treatment group ($p = 0.6$). Twenty eight (78%) patients in the enrasentan treatment group reported no change in their condition compared with 26 (72%) in the enalapril treatment group ($p = 0.6$). No patient in the enalapril group required hospitalisation for cardiovascular related reasons compared with 8% in the enrasentan group ($p = 0.08$). The addition of a diuretic was required by 8% of patients in the enrasentan group compared with 6% in the enalapril group ($p = 0.7$).

Patient HF self assessment

For the single criterion of patient self reported symptoms, by study end 38% of patients in the enalapril group reported feeling better (mildly to greatly improved) compared with 28% in the enrasentan group ($p = 0.4$), and 9.4% in the enrasentan group felt slightly worse than at baseline compared with 3.1% in the enalapril group ($p = 0.3$).

Figure 2 Comparison of change in cardiac index after six months' treatment.

Figure 3 Comparison of change in neurohormone concentrations after six months' treatment. BNP, brain natriuretic peptide; NE, noradrenaline (norepinephrine).

Adverse events

Overall, five patients (14%) in the enrasentan group had a laboratory value of potential clinical concern compared with six (17%) in the enalapril group ($p = 0.7$). No patients were withdrawn from the study due to abnormal laboratory values. Twenty patients had at least one vital sign that met the criteria for potential clinical concern, eight (22%) in the enrasentan group and 12 (33%) in the enalapril group ($p = 0.3$). Thirty four (94%) patients in the enrasentan group reported at least one adverse event during the study period compared with 31 (86%) in the enalapril group ($p = 0.2$) (table 5).

Two patients died during the study. One patient had received enalapril 20 mg and died of an acute coronary syndrome 19 days after the last dose and the other patient received enrasentan 90 mg and died of endocarditis 34 days after the first dose and 10 days after premature cessation of study medication; both cases were considered unlikely to be related to the study medication. Seven patients had serious non-fatal adverse events after randomisation. In the uptitration phase 3 patients in the enrasentan group reported endocarditis, pneumonia, or thrombophlebitis; one patient in the enalapril group reported angina ($p = 0.3$). In the maintenance phase, four patients, all in the enrasentan group, experienced serious adverse events (chest pain, deep venous thrombosis, sinusitis, and dyspepsia) compared with none in the enalapril group ($p = 0.02$). The same patient with thrombophlebitis in the uptitration phase experienced deep venous thrombosis in the maintenance phase. Thus, in total, six (16.7%) patients in the enrasentan group experienced serious adverse events that the study investigators deemed to be potentially attributable to study medication compared with one (2.8%) in the enalapril group ($p = 0.02$).

Table 5 Adverse events occurring in greater than 10% of patients in either group during the uptitration and maintenance phases

Adverse event	Frequency of adverse event	
	Enrasentan	Enalapril
Uptitration phase		
Fatigue	5 (13.9%)	5 (13.9%)
Flushing	4 (11.1%)	0
Maintenance phase		
Respiratory disorder	5 (13.9%)	4 (11.1%)
Viral infection	1 (2.8%)	5 (13.9%)
Back pain	4 (11.1%)	0

Adverse events resulted in six patients withdrawing prematurely from the study, three in each treatment group ($p = 0.7$)—these were the two patients who died and one patient with a serious non-fatal adverse event (deep venous thrombosis). Three patients were withdrawn with non-serious events considered to have a probable or suspected relation to the study medication: dizziness and cardiac failure in one patient receiving enrasentan 30 mg and cough in two patients receiving enalapril 20 mg ($p = 0.6$).

DISCUSSION

This study is the first head to head comparison of monotherapy with an endothelin antagonist versus monotherapy with an ACE inhibitor in asymptomatic patients with LV dysfunction. Previous studies have examined the effects of endothelin antagonists compared with placebo on a background of treatment with an ACE inhibitor and a diuretic and usually in more advanced cases of HF. The key finding was the relative inability of monotherapy with enrasentan to prevent an increase in LV EDVI over six months compared with monotherapy with enalapril. The reduction in BNP with enrasentan was also less than that observed with enalapril, and changes in other neurohormones were likewise more favourable with enalapril. Although the study was not devised to investigate clinical outcomes, in general these tended to favour enalapril. Overall, these data suggest that enrasentan is less able than enalapril to retard adverse ventricular remodelling in asymptomatic patients with LV dysfunction.

The precise role of endothelin in the pathophysiology of chronic HF is still to be defined, but it is already clear, from this study and others, that the relation is much more complex than initially expected. Although increased plasma concentrations of endothelin appear to be associated with more severe cardiac dysfunction, higher vascular resistance, worse symptoms, and a poorer outcome, our study and others suggest that it is far from clear that interfering with activation by endothelin receptor blockade is beneficial. The adverse remodelling seen with enrasentan is in accord with the adverse mortality reported in the ENCOR (enrasentan cooperative randomised evaluation) study and suggests that the LV EDVI in the current study, which was relatively small, was an appropriate surrogate for the outcome in the larger ENCOR study.¹⁰ However, the mechanism for the adverse remodelling in the LV EDVI in patients taking enrasentan is not clear. Several possible factors may contribute to the adverse remodelling. One possibility is the effect on blood pressure, as enalapril is known to lower blood pressure in HF. In the current study, however, the enrasentan and enalapril groups did not differ significantly in blood pressure at baseline or over the treatment period. Another possibility is that enrasentan caused a fall in haemoglobin concentration as has been observed in other studies of endothelin antagonists¹¹ but, in this study, clinically haemoglobin concentration did not change significantly. There is some evidence that endothelin A receptor blockade may reduce myocardial contractility in patients with less severe ventricular dysfunction, when the direct effects of endothelin on the myocardium may not be offset by the benefits of peripheral vasodilatation.¹² However, the cardiac index increased with enrasentan compared with enalapril, which appeared to be due to an increase in stroke volume, as the heart rate did not change. This may reflect greater vasodilatation with the endothelin antagonist. Alternatively, a more speculative mechanism is an increase in pulmonary shunting with the endothelin antagonist. There is some evidence for this in a study of tezosentan in acute HF, where the endothelin antagonist caused a drop in arterial oxygen saturation.¹³ If such an effect occurred with enrasentan, then

it may explain the increase in cardiac output seen, combined with the increase in LV EDVI and an adverse outcome. The minor effects on blood pressure and haemoglobin may contribute to this, although a larger study would be required to establish this. Another possibility is the receptor selectivity of the drug. Enrasentan is more selective for the endothelin A receptor but at the doses used in this study it would also have blocked endothelin B receptors on vascular smooth muscle and the endothelium.¹⁰ Blockade of endothelial endothelin B receptors results in a rise in plasma endothelin, which can have adverse consequences in the absence of adequate blockade of endothelin A receptors.¹⁴ The dosage of enrasentan used in this study was based on a combination of animal studies and human safety and efficacy data, and matched the dose used in the ENCOR trial.¹⁰ A different dose or a more selective endothelin A receptor antagonist would possibly have fewer adverse effects, although recent reports suggest that this is not the case.¹⁵ However, an alternative explanation is that none of the endothelin antagonists used so far is selective enough and doses of relatively selective agents may have been used at such a high dose that selectivity was lost.³ Lastly it is possible that endothelin 1 is a protective factor against myocardial cell apoptosis in HF and endothelin antagonists may confound this process.¹⁶ The observed changes in LV volumetric measurements correlate with the changes in LV mass and therefore suggest that true remodelling effects are being assessed rather than the impact of active drug induced load related effects.

Other endothelin antagonist trials in HF

The chronic effects of endothelin antagonists have been evaluated in patients with symptomatic HF. The ENCOR trial randomly assigned 419 patients with HF (NYHA class II–III) and an EF of $< 35\%$ on standard treatment to two doses of enrasentan, placebo, or high dose enalapril.¹⁰ After nine months of treatment the composite end point had not improved (improvement in either NYHA functional class or global patient assessment, or both). The clinical status of the enrasentan group worsened compared with placebo with an increased rate of hospitalisation and withdrawals from study medication due to adverse effects including deterioration of HF. There was a trend towards progressive LV dysfunction with LV dilatation and increased total mortality with enrasentan. No differences between enrasentan doses were noted. Subsequently, in the REACH-1 (randomised endothelin antagonism in chronic heart failure with bosentan) trial, ENABLE 1 and 2 (endothelin antagonist bosentan for lowering events),¹⁷ and the EARTH study (endothelin A receptor antagonist trial in heart failure trial),¹⁵ the results of treatment with endothelin antagonists have also been disappointing in symptomatic HF and have not mirrored the highly promising effects in animal disease models. Notably, however, all of these studies have assessed symptomatic patients predominantly in NYHA class II–III with more advanced HF. An unaddressed question from these earlier trials was whether we had reached the ceiling with neurohumoral blockade in chronic HF. Would endothelin antagonists have been successful drugs in HF, if they had been introduced before ACE inhibitors, β blockers, and spironolactone? Does the early introduction of an endothelin antagonist help to halt some of the progression in HF in those patients with the mild form of the disease? In animal models, following chronic angiotensin infusion, both angiotensin blockade and endothelin A blockade appear to exert comparable protective effects.¹⁸ Accordingly, endothelin blockade may be less efficacious on the background of ACE or angiotensin inhibition. To test this hypothesis a direct comparison with ACE inhibitors is required as was done with β blockers in the CARMEN (carvedilol ACE inhibitor

remodelling mild CHF evaluation) study.¹⁹ The present study is unique in comparing ACE inhibitors versus an endothelin antagonist in an asymptomatic population with a mild form of HF to address some of these questions.

Limitations

There was no placebo group and therefore the size of benefit achieved with enalapril is unknown. It is possible that both enrasentan and enalapril would have shown beneficial effects on remodelling compared with placebo, despite our data showing that enrasentan is less effective than enalapril. Data from a radionuclide substudy of the SOLVD (studies of left ventricular dysfunction) trial suggest that, over six months, LV EDVI should increase by about 3 ml/m², which is similar to the change observed with enrasentan in our study, although mean baseline LV EDVI (129 ml/m²) was much higher in SOLVD.²⁰ The patients in the current study had systolic dysfunction with impaired EF as determined by echocardiographic criteria. After randomisation, EF was determined again at baseline by CMR and was in the lower range of normal. This discrepancy is partly methodological, a recent study indicating that CMR may give higher EF values than those obtained by echocardiography.²¹ The echocardiographic EF was chosen for screening rather than the CMR measurement to reflect routine clinical practice. Echocardiography has also formed the basis for inclusion in previous large scale multicentre HF trials.²² There was a disparity in BNP concentrations at baseline and changes that may affect the differences for this parameter between the two drug regimens. An exclusion criterion for the study was use of an ACE inhibitor or angiotensin II receptor antagonist in the six weeks before enrolment. Potentially, however, if patients had discontinued such treatment in the three to six months before the study, some decompensation may have occurred producing adverse remodelling. No difference was noted, however, in such withdrawal between the two groups. Serial endothelin concentrations were not measured reflecting the poor correlation between overall endothelin concentrations and response to treatment. In addition, there is at present little evidence to indicate that reduction in endothelin 1 is a useful marker of treatment success.

Conclusion

In this unique study of the comparative effects of the mixed endothelin A/B receptor endothelin antagonist enrasentan with an ACE inhibitor, enalapril, in asymptomatic patients with LV dysfunction, the results suggest that enrasentan does not appear to have favourable effects on ventricular remodelling and is not an effective substitute for an ACE inhibitor.

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