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Mending the Broken Heart: A Neprilysin Inhibitor for Heart Failure

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ABSTRACT

Sacubitril/valsartan, an angiotensin-receptor neprilysin inhibitor, was recently approved by the United States Food and Drug Administration for reduction of morbidity and mortality in patients with heart failure with reduced ejection fraction. Sacubitril is the first drug in the neprilysin inhibitor class that assists with volume regulation by inhibiting the breakdown of brain natriuretic peptide. When compared with an angiotensin-converting enzyme inhibitor, sacubitril/valsartan demonstrated reductions in rehospitalization and all-cause mortality. Sacubitril/valsartan could replace angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

Keywords: Entresto, heart failure, neprilysin inhibitor, reduced ejection fraction, sacubitril/valsartan

INTRODUCTION

Heart failure (HF) affects approximately 5.7 million people and has a mortality rate of approximately 50% within 5 years of diagnosis.[1] After 15 years without a new medication for this disease, 2 novel agents for the treatment of HF with reduced ejection fraction (HFrEF) have recently been granted approval by the United States Food and Drug Administration (FDA). Reduction of mortality and morbidity are the goals of treatment of this chronic and progressive disease. Only 1 of the 2 new agents has a proven mortality benefit—that is, a combination medication, sacubitril/valsartan (trade name: Entresto, Novartis Pharmaceuticals, East Hanover, NJ).

CURRENT HF TREATMENT

The foundation of HF treatment that reduces morbidity and mortality currently consists of angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), specific beta-blockers, and aldosterone antagonists.[1] These treatments revolve around blocking 2 neurohormonal systems: the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Use of these agents at target doses is considered to be the standard of care in HF treatment, referred to by the American College of Cardiology Foundation/American Heart Association as guideline-directed medical therapy (GDMT).[1]

NATRIURETIC PEPTIDES AND NEPRILYSIN

Brain natriuretic peptide (BNP) and amino-terminal pro–B-type natriuretic peptide (NT-proBNP) are considered the "gold standard" in the detection of heart failure and in the determination of patient prognosis and disease progression.[2-6]

The natriuretic peptide system is responsible for volume and pressure homeostasis- promoting vasodilation, diuresis, natriuresis, and regulation of cardiac remodeling via antiproliferative and antihypertrophic actions. Activities of the RAAS and SNS are also downregulated. The effects of this regulatory system can be seen in the kidneys, central nervous system, and cardiovascular system. In patients with HFrEF, improvement in hemodynamic parameters can be seen by an increase in urine output and a decrease in preload and systemic vascular resistance, leading to an overall improvement in cardiac output.

Natriuretic peptides are cleared by 2 main mechanisms. The first involves natriuretic peptide clearance receptor, which degrades and internalizes the peptides. The peptides can also be broken down by enzymatic degradation by neprilysin, also called neutral endopeptidase. Neprilysin can also act on other peptides, including angiotensin II and bradykinin.[7]

OVERVIEW OF NEPRILYSIN INHIBITION: A NEW CLASS OF PHARMACOLOGIC AGENTS

Some of the early trials of sole neprilysin inhibition demonstrated encouraging outcomes in terms of volume regulation, but lacked the improvement in hemodynamic parameters (systemic vascular resistance) essential in the management of heart failure patients.[7] Because neprilysin is not cardiospecific, it was necessary to pair it with another pharmacologic class that would counteract the vasoconstriction caused by lack of angiotensin II breakdown. The combination of neprilysin and an ACE-I demonstrated adequate blood pressure control, but also had a higher incidence of angioedema. This is thought to be due to the accumulation of bradykinin from the dual inhibition of neprilysin and the ACE-I, as well as the inhibition of aminopeptidase, another enzyme involved in bradykinin metabolism.[5,8]

Sacubitril/valsartan provides a novel approach in the complementary blockade and augmentation of the neurohormonal circuit by neprilysin inhibition and angiotensin blockade. This combination has less inherent risk of angioedema than a neprilysin inhibitor combined with an ACE-I. A twice-daily dosing scheme is needed to ensure sustained inhibition over a 24-hour period.

Sacubitril blocks neprilysin and prevents the breakdown of BNP; therefore, the measured levels will be higher. This does not represent a worsening of HF. Because NT-proBNP is not a substrate of neprilysin, levels will remain unaffected. For clinicians using natriuretic peptide–guided therapy, NT-proBNP should be used over BNP alone.

PARADIGM-HF

The trial that enabled sacubitril/valsartan to gain FDA approval, PARADIGM-HF, proved the superiority in morbidity and mortality for sacubitril/valsartan versus enalapril in patients with HFrEF of $\leq$ 35%.[9] The study was a double-blind, randomized, parallel trial with 8,442 patients who had New York Heart Association (NYHA) class II, III, or IV. Patients were included in the study if they were $\geq$ 18 years old with an ejection fraction (EF) of $<$ 35% with either a BNP $>$ 150 pg/mL or NT-proBNP $>$ 600 pg/mL. All patients had to be on a stable dose of a beta-blocker and ACE-I or ARB (equivalent to enalapril 10 mg/d) for 4 weeks before the study. Of note, in addition to the study drug, only half of the patients included in the study were on $\geq$ 50% of the target dose of beta-blockers.[10] Patients were excluded if they had a systolic blood pressure of $<$ 100 mm Hg, renal dysfunction, serum potassium $>$ 5.2 mmol/L, or history of angioedema or intolerance to ACE-Is or ARBs.

Patients who met the inclusion criteria received enalapril 10 mg twice daily for 2 weeks. If tolerated, patients were assigned to receive either sacubitril/valsartan (initial dose 100 mg twice daily, increased to target dose of 200 mg twice per day) or enalapril 10 mg twice per day. The primary outcome was a composite of HF hospitalization and cardiovascular death. The majority of patients in the study were NYHA class II (71.6%) or class III (23.1%). The primary composite outcome showed the superiority of sacubitril/valsartan to enalapril, with 914 (21.8%) patients in the study group versus 1,117 (26.5%) in the enalapril group having more events ($P < .001$, 95% confidence interval 0.73 to 0.87, number needed to treat (NNT) 21). Sacubitril/valsartan showed a significant benefit in deaths from cardiovascular causes when compared with enalapril (13.3% vs. 16.5%, $P < .001$, 95% confidence interval 0.71-0.89, NNT 32). With regard to first hospitalization from worsening HF, sacubitril/valsartan was significantly better, with only 12.8% of patients readmitted compared to 15.6% with enalapril ($P < .001$, 95% confidence interval 0.71-0.89).

The sacubitril/valsartan group had a higher percentage of patients who had hypotension (14%) and angioedema (0.4%), although all patients in the study had previously tolerated ACE inhibition. The sacubitril/valsartan group had a lower frequency of renal impairment (4.8%), hyperkalemia (20.4%), and cough (11.3%) compared with the enalapril group.

CASE STUDY 1

A 70-year-old African-American woman is following up from hospitalization for acute new-onset HFrEF. Her echocardiogram revealed an EF of 35%. BNP level at discharge was 500 pg/mL. Renal function is normal with serum creatinine 0.9 mg/dL (normal 0.6-1.3 mg/dL) and potassium 4.1 mmol/L (normal 3.5-5.1 mmol/L). Her past medical history includes