ARxCH
Annual Review of Changes in Healthcare

Entresto: An Overview for Pharmacists

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Learning Objectives
•To inform pharmacists of a new agent used in the treatment of NYHA class II-IV heart failure
•To inform pharmacists of clinical trial results supporting efficacy and safety of Entresto
•To inform pharmacists of alternative/combination target sites/mechanisms of Entresto
•To inform pharmacists of common adverse effects associated with Entresto

Abstract

Entresto is a new drug that was developed for NYHA stage II heart failure. It was evaluated through the PARAMOUNT-HF and PARADIGM trials and showed some benefits to patients suffering from heart failure. There are many products that are approved for the treatment of heart failure to either decrease morbidity/mortality or provide symptom relief. It is a serious disease state and provides pharmacists with an opportunity to make appropriate recommendations in order to benefit patients. This review will discuss different characteristics of Entresto and some of the evidence associated with its use.

Not only do 5.7 million people in the United States have heart failure, but one in nine deaths in 2009 were from heart failure.[1] Roughly half of all people who are diagnosed with heart failure die within five years.[1] Heart failure is also associated with a total national cost of approximately $30.7 billion.[1] Coronary heart disease, hypertension, and diabetes are the most common comorbidities that predispose a person to developing heart failure.[1] This disease state is a serious issue facing the United States, and it is imperative that work be done to combat this condition.

Heart failure is defined by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) as impairment in the ability of the heart to eject blood or perform ventricular filling.[2] This damage may be in the endocardium, pericardium, heart valves, or other anatomical areas. Typical signs and symptoms result from peripheral edema and pulmonary congestion which leads to dyspnea and fatigue. The New York Heart Association (NYHA) defines stages of heart failure based on physical activity. Stage I indicates there is no limit on physical activity, whereas stages II, III, and IV specify slight limitation, marked limitation or the inability to engage in any physical activity without severe symptoms, respectively. Pharmacotherapy has historically targeted the renin-angiotensin-aldosterone system when treating heart failure. Other heart failure treatments include diuretics and beta-antagonists.[2]

Angiotensin Converting Enzyme (ACE) inhibitor therapy has been the foundation of heart failure treatment due to the significant decreased risk of death shown in clinical studies.[3] Angiotensin receptor blockers (ARBs) have typically been reserved for patients who suffered from adverse side effects or in patients who could not tolerate ACE inhibitors. Entresto (sacubitril/valsartan) contains a new product called sacubitril which acts as a neprilysin inhibitor in addition to valsartan (an ARB). Neprilysin is an enzyme responsible for the degradation of several endogenous vasoactive peptides including natriuretic peptides and bradykinin. Eliminating the degradation of these endogenous vasoactive peptides ultimately results in increased vasodilation, natriuresis, and diuresis. Valsartan blocks the binding of angiotensin II to AT1 receptors. Ultimately this blocks the vasoconstrictive and aldosterone stimulating effects of angiotensin II.[5]

Entresto is primarily indicated for use in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization.[2] Entresto should always be administered in conjunction with other heart failure therapies and in place of other ACE/ARB therapies.[2]

Pregnant women should avoid Entresto as it is a known teratogen. The black box warning states that this drug may cause fetal abnormalities and therefore, it is necessary to counsel women of child-bearing age about this important risk. Lactating women are advised not to take Entresto as it was found in animal trials to be secreted in breast milk. It is also important to inform patients prescribed Entresto to report side effects including: signs/symptoms of kidney dysfunction (urinary retention, blood in urine, change in amount of urine passed, or weight gain),

signs/symptoms of high potassium (abnormal heartbeat, confusion, dizziness, passing out, weakness, shortness of breath, numbness or tingling feeling), loss of strength and energy, angioedema, or dry hacking cough.[5]

Dosage strengths (sacubitril/valsartan respectively) vary from 24/26mg, 49/51mg, and 97/103mg and are referred to as 50mg, 100mg, and 200mg respectively.[4] The recommended dose to titrate to is the 97/103mg strength. Entresto is not recommended in severe liver impairment, and renal adjustments need to be made when estimated glomerular filtration rate (eGFR) is reduced to less than 30 mL/min.[5] Patients who are currently taking an ACE-inhibitor should not be started on Entresto until 36 hours after their last dose (washout period).[2]

Knowledge Check:
Entresto therapy aims to replace which of the following current HF therapies?

A) ACE/ARB therapy in NYHA class II-IV HF patients
B) ACE/ARB therapy in all HF patients (NYHA class I-IV)
C) ACE/ARB therapy ONLY in severe HF cases (NYHA class IV)
D) None of the above

Answer: A

The PARADIGM-HF trial was a prospective comparison of Angiotensin–Neprilysin Inhibition compared to an ACE inhibitor (enalapril) to determine the impact on global morbidity and mortality in heart failure. This study was designed to provide evidence to support the replacement of ACE inhibitors or ARBs with Entresto in the management of chronic heart failure.[6] In this trial, the primary outcome was a composite of death from cardiovascular causes or first hospitalization for heart failure.[6] Over eight thousand patients with NYHA class II-IV symptoms with EF ≤40% were included (4187 patients were randomly assigned to Entresto treatment, and 4212 received enalapril for the intention-to-treat analysis).[6] Death from cardiovascular causes or hospitalization for heart failure occurred in 914 patients (21.8%) in the Entresto group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the Entresto group = 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001).[6] The study concluded that Entresto was superior to ACE inhibition alone and prevented one or more cardiovascular deaths or heart failure hospital admissions for every 21 patients treated for two years when compared to enalapril.[6] The study stated that the superiority of Entresto over enalapril was not accompanied by important safety concerns and that fewer patients stopped their study medication in the Entresto group than in the enalapril group because of an adverse reaction.[6]

A second trial called the PARAMOUNT study was a prospective comparison trial. PARAMOUNT was a phase II randomized, parallel grouped, double blind, multicenter trial that observed patients with NYHA heart failure preserved ejection fraction (HFpEF) of 45% or higher and pro-brain naturieretic peptide (pro-BNP)

greater than 400 pg/mL.[7] Elderly females were a majority of the study participants with about one quarter of them having atrial fibrillation as a comorbidity. Roughly half of all patients in the trial had diabetes and some form of kidney dysfunction.[7] Patients received Entresto (titrated to a strength of 200mg) twice daily or valsartan (160 mg) twice daily for 36 weeks. Pro-BNP is a peptide marker of heart failure and therefore was a primary outcome. This peptide marker was significantly reduced at 12 weeks in the Entresto group compared with the valsartan group. The Entresto group's pro-BNP dropped by 178 pg/ml and the valsartan group's pro-BNP dropped by 27 pg/ml on average. Adverse drug events were notably similar amongst groups taking Entresto and those taking only valsartan.[7]

Based on these studies, Entresto has shown to be an important drug for the future and appears to be an asset in the treatment of heart failure as a replacement to traditional ACE/ARB therapy. According to the PARAMOUNT and PARADIGM trials, patients who take Entresto may have better health outcomes on average versus those who do not. Pharmacist involvement in patients with heart failure is an important aspect of care for these patients in the future. A focus on the relevance of these trials and proper recommendations to providers may help patients in the United States with heart failure achieve better outcomes.

References

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