International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Effect of sacubitril/valsartan on cardiac filling pressures in patients with left ventricular systolic dysfunction

Zubair Khan *, Gunjan Gholkar, Sunit Tolia, Herman Kado, Marcel Zughaib

Department of Cardiology, Providence-Providence Park Hospital, Southfield, MI 48075, USA

ARTICLE INFO

Article history:
Received 15 February 2018
Accepted 19 March 2018
Available online xxxx

Keywords:
Sacubitril/valsartan
CardioMems
Congestive heart failure
Cardiac filling pressure

ABSTRACT

Background: Sacubitril/valsartan is the newest neurohormonal agent approved for therapy in patients with heart failure with reduced ejection fraction (HFrEF). Little is known about its acute and incremental hemodynamic effects. We aimed to evaluate the change in hemodynamic profiles measured using an implanted monitoring device in HFrEF patients initiated on sacubitril/valsartan therapy.

Methods: We prospectively enrolled 13 subjects with HFrEF and pre-implanted CardioMEMS™ device on maximally tolerated guideline-directed medical therapy and no contraindications to sacubitril/valsartan therapy. Transmitted pulmonary artery diastolic pressures (PAdP) from CardioMEMS™ were averaged and compared for one week before and after initiation of sacubitril/valsartan, as well as after change in medication strength and finally at three months.

Results: Sacubitril/valsartan dose increase was tolerated in 7/13 subjects with drug discontinuation in one subject after a week due to renal dysfunction. There was a significant reduction in mean PAdP after sacubitril/valsartan initiation compared to standard therapy (20.8 vs 18.3 mm Hg, $p = 0.020$). No further PAdP reduction was noted after sacubitril/valsartan dose increase (19.7 vs 20 mm Hg, $p = 0.673$) and at 3-month follow-up compared to baseline (20.8 vs 19.2 mm Hg, $p = 0.352$).

Conclusions: Sacubitril/valsartan causes an acute reduction mean pulmonary artery pressures after initiation. However, no incremental reduction in PAdP was noted after dose increase and short-term follow-up. The current study demonstrates the utility of CardioMems™ device to study the drug's impact on hemodynamic profile in both short- and long-term follow-up.

1. Introduction

Heart failure (HF) is a worldwide epidemic associated with substantial morbidity and five-year mortality approaching close to 50% [1]. In the United States, it is the leading cause of death and one of the most common diagnosis for hospital readmissions [2]. Timely diagnosis and treatment of heart failure is paramount in improving patient's quality and duration of life. Besides non-pharmacologic therapies such as lifestyle and behavioral changes, pharmacologic treatments for heart failure typically include a combination of drugs including renin-angiotensin-aldosterone system (RAAS) inhibitors, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB), in addition to beta-blockers, diuretics, aldosterone receptor antagonists, inotropes, and digoxin [3,4]. Recent guidelines on the management of heart failure now suggest replacement of ACEi/ARB by an angiotensin receptor/neprilysin inhibitor (ARNI) in optimally treated appropriately selected patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF) [3,4]. The latest recommendation stems from the additional morbidity and mortality benefit noted with the only approved drug in its class, sacubitril/valsartan in the Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial [5]. Treatment with sacubitril, a neutral endopeptidase that degrades endogenous vasoactive peptides, increases circulating levels of natriuretic peptides, which have been shown to facilitate natriuresis and vasodilation.

Hemodynamic assessment has long been used in clinical practice for objectively defining the efficacy of new pharmacologic therapies for

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ADHF, Acute decompensated heart failure; BNP, Brain natriuretic peptide; ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin II receptor blockers; ARNI, Angiotensin receptor/neprilysin inhibitor; CHAMPION, CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure; CHF, Congestive heart failure; ESC, European Society of Cardiology; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; LAP, Left atrial pressure; LV, Left ventricle; NYHA, New York Heart Association; PA, Pulmonary artery; PAdP, Pulmonary artery diastolic pressure; PARADIGM-HF, Prospective Comparison of ARNI With ACEi to Determine Impact on Global Mortality and Morbidity in Heart Failure; PAsP, Pulmonary artery systolic pressure; RAAS, renin-angiotensin-aldosterone system; PARADISE-MI, Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI; PCWP, Pulmonary capillary wedge pressure; TRANSITION, pre-discharge and posT-discharge tReatment initiation with sacubitril/valsartan in heArt failure patieNtS with reduced ejectIon-fracTion hospItalised for an acute decOmpensation eveNt.

* Corresponding author at: Department of Cardiology, Providence-Providence Park Hospital, 16001 W.Nine Mile Road, Southfield, MI 48075, USA.
E-mail address: zubair.khan@ascension.org (Z. Khan).

https://doi.org/10.1016/j.ijcard.2018.03.093
0167-5273/

heart failure. However, the acute hemodynamic benefits noted with the pharmacologic agents have not translated into long-term clinical benefits despite maintenance of hemodynamic improvement [6]. ACEi have been shown to have several acute and sustained hemodynamic effects including increase in cardiac output and stroke volume and reduction in systemic vascular resistance as well as pulmonary capillary wedge pressure. These hemodynamic effects are particularly beneficial in the presence of left ventricular (LV) dysfunction and are associated with improvement in HF-related morbidity and mortality [7].

Results from previous small clinical trials involving patients with hypertension or heart failure with preserved ejection fraction have showed that sacubitril/valsartan had hemodynamic and neurohormonal effects that were greater than those of ARB alone [8,9]. Nevertheless, there remains a paucity of data regarding incremental acute and long-term hemodynamic effects of composite therapy with sacubitril/valsartan.

CardioMEMS™ HF system is a small microchip inserted transvenously in the pulmonary artery and can chronically monitor pulmonary pressures. The information from CardioMEMS™ is remotely transmitted by the patient to a website where it is reviewed by the HF team, who can intervene to adjust diuretics and other medications by phone to avert decompensation and re-hospitalization. In the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in Class III Heart Failure) trial, this strategy led to significant decreases in pulmonary artery (PA) pressures, fewer patients hospitalized for HF, more days alive outside of the hospital, improved quality of life, and a trend toward improved mortality in the treatment than in the control group [10]. The device received FDA approval in mid-2014 for HF with New-York Heart Association (NYHA) class III symptoms. In appropriately selected patients, CardioMEMS™ provides a novel approach to monitor the hemodynamic effects various pharmacological therapies in real-time in a non-hospital based setting. In this study, we aimed to examine the acute and short-term effect of sacubitril/valsartan on cardiac filling pressures in patients with HFrEF with pre-implanted CardioMEMS™ implantable sensor.

2. Methods

In our prospective, nonrandomized, single-center pilot study, we enrolled 13 subjects with HFrEF (defined as left ventricular ejection fraction of ≤35% assessed within one year prior to enrollment) on maximally tolerated medical therapy with NYHA class II-III symptoms and pre-implanted CardioMEMS™ device. Exclusion criteria were symptomatic hypotension, SBP <100 mm Hg at screening, estimated glomerular filtration rate (eGFR) below 30 ml per min per 1.73 m^2 of body surface area, serum potassium level of >5.2 mmol per liter, prior use of sacubitril/valsartan and history of angioedema/other contraindications or unacceptable side effects to ACEi/ARB. Written consent explaining research protocol, risk and benefits was obtained from each participant. Subject transmitted data for pulmonary artery systolic pressure(PAsP), pulmonary artery diastolic pressure(PAdP) and mean pulmonary artery pressure (mPAP) were obtained from CardioMEMS™ patient care network (Merlin.net™). The readings were averaged for the week prior to, the week after initiation of sacubitril/valsartan and the week after dose titration if tolerated and finally at 3-month follow up. A 48-h ACEi/ARB washout period was allowed prior to initiation of sacubitril/valsartan and transmission of CardioMEMS™ data. All subjects were assessed in the clinic at one week to assess drug tolerance with assessments of renal function and potassium levels and maintained their routine CardioMEMS™ transmissions during the follow-up period. Changes in medical therapy and incremental dosing adjustment for sacubitril/valsartan were left at physician's discretion during the follow-up duration based on clinical symptoms and CardioMEMS™ data.

Pairwise comparisons were conducted to evaluate the null hypothesis that there is no change in average PA pressures when measured before, after sacubitril/valsartan initiation or dose increase or at 3-month follow-up. Significance was determined as a p- value < 0.05. Summary statistics are presented as N (%) for categorical variables; continuous variables are presented as mean ± SD. All statistical analyses were performed using IBM SPSS, version 21.0.

3. Results

Baseline demographic, anthropomorphic, and clinical history are presented in Table 1. All subjects were on maximally tolerated guideline directed medical therapy for HFrEF including ACEi/ARB therapy and maintenance diuretic therapy presented in Table 2. All but one subject was started on an initial dose of 24/26 mg twice daily. An increased dose of sacubitril/valsartan dose to 49/51 mg from 24/26 mg could be tolerated in 7 out of 12 subjects with symptomatic hypotension and rise in creatinine being the limiting factors in the remaining subjects. One subject was initiated on baseline dose of 49/51 mg with no further increase during follow-up period. One subject could not tolerate the medication with significant worsening in renal function at one-week follow-up and was excluded from analysis. No further up-titration in ARNI dose was performed in any of the enrolled subjects during the follow-up period. No changes were made in baseline medications in 9 out of the remaining 12 subjects; two subjects required an increase in diuretic dose while maintenance diuretics were held for 48 h in one subject for obstructive uropathy resulting from recurrent renal calculi. None of the subjects had heart failure related ER visits or hospital admissions during the follow-up duration.

Table 1
Baseline characteristics.

		$N = 13$
Age *(mean ± SD)*		73 ± 10
BMI *(mean ± SD)*		28.3 ± 6.5
Male gender *(n, %)*	*Male*	8 (61%)
Race *(n, %)*	*Caucasian*	6 (46%)
	African–American	7 (54%)
Hypertension *(n, %)*		13 (100%)
Hyperlipidemia *(n, %)*		13 (100%)
Diabetes Mellitus *(n, %)*		6 (46%)
Coronary Artery Disease *(n, %)*		10 (77%)
Atrial Fibrillation/Other arrhythmias *(n, %)*		4 (31%)
Chronic Kidney Disease *(n, %)*		4 (31%)
LVEF ≤ 35% *(n, %)*		13 (100%)
ICD *(n, %)*		8 (61%)
CRT *(n, %)*		1 (8%)

Abbreviations: CRT = Cardiac resynchronization therapy; ICD = Implantable cardioverter-defibrillator; LVEF = Left ventricular ejection fraction.

A decrease in systolic blood pressure was noted at one-week follow-up after sacubitril/valsartan initiation compared to baseline with ACEi/ARB therapy but did not reach statistical significance (Δ8.7 ± 21, from 133 to 124 mm Hg, $p = 0.188$). Follow-up pairwise comparisons showed a significant reduction in PAdP in the week following sacubitril/valsartan initiation compared to the week prior on ACEi/ARB therapy (Δ2.5 ± 3.1 mm Hg, $p = 0.020$) with similar results for averaged PAsP (Δ3.6 ± 4.9 mm Hg, $p = 0.027$) and mPAP (Δ3.2 ± 3.9 mm Hg, $p = 0.015$) (Fig. 1). There was no further PAdP reduction noted in the 7 subjects tolerating the increased dose of 49/51 mg from 24/26 mg twice daily (Δ-0.29 ± 1.7 mm Hg, $p = 0.673$) (Fig. 2). The hemodynamic response in average PA pressures was relatively sustained with the trend in levels continuing to be lower than baseline values (Fig. 1).

4. Discussion

Earlier studies have identified abnormal hemodynamics associated with acute decompensated heart failure (ADHF), especially left

Table 2
Baseline medical therapy prior to initiation of sacubitril/valsartan.

	N = 13
ACE-i or ARB *(n, %)*	13 (100%)
Beta-Blockers *(n, %)*	10 (77%)
Aldosterone Receptor Blocker *(n, %)*	8 (61%)
Hydralazine/isosorbide dinitrate *(n, %)*	2 (15%)
Calcium channel blocker *(n, %)*	2 (15%)
Diuretics *(n, %)*	13 (100%)
Other vasodilator *(n, %)*	0 (0%)
Digoxin *(n, %)*	0 (0%)

Abbreviations: ACE-i = Angiotensin converting enzyme inhibitor; ARB = Angiotensin receptor blocker.

Please cite this article as: Z. Khan, et al., Effect of sacubitril/valsartan on cardiac filling pressures in patients with left ventricular systolic dysfunction, Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2018.03.093