Original Research Article

Sacubitril/valsartan in advanced heart failure: is it just a matter of contractility or are there effects on the pulmonary circulation? A real life monocentric experience.

ABSTRACT

Background: Sacubitril/valsartan (S/V), an angiotensin receptor neprilysin inhibitor (ARNI), is the first drug to demonstrate a mortality benefit in patients with chronic heart failure and reduced ejection fraction. S/v had a 20% reduction in the primary composite endpoint of cardiovascular death or heart failure hospitalization, compared with subjects receiving enalapril. However, the mechanisms are not clear. The aim of this prospective, non-randomized study was to assess the clinical and instrumental effects of this agent in patients with HFrEF and pulmonary hypertension.

Methods: To investigate the effects of S/V in HFrEF, we selected 40 consecutive patients (31 males, 9 females, mean age 64±19 years) in the NYHA class II-III, because they had left ventricular ejection fraction ≤35% at echocardiography. Etiology: 22 CHD, 3 Myocarditis, 15 IDCM

Results: 2 patients took the maximum dose of 97/103 mg, 2 stopped the therapy due to a creatinine increase, all the others took the dose of 49/52 mg. During a mean ± SD follow-up of 24±6 months, no patients died. PASP decreased from 42.71 to 36 mm/Hg (p <0.0001); 6MWT improved from 402 m to 453 m (p <0.0001). Mean LVEF increased from 28.9% to 31.5% p <0.005); NYHA mean class improved from 1.95 to 1.70. An AICD was implanted in 20 patients.

Conclusion: These preliminary data suggest that in patients with severe heart failure, S/V is able to improve 6MWT and PASP, even in the absence of a significant improvement of ventricular contractility. S/v may reduce the fluid retention and pulmonary vasoconstriction that contribute to heart failure symptoms.

Keywords: Sacubitril/Valsartan; Pulmonary Circulation; Congestive Heart Failure.

Background

In patients with left ventricular dysfunction, the presence of Pulmonary Hypertension (PH) is known to be associated with a poor prognosis and limited efficacy of conventional medical treatments. [1, 2] There is currently no approved treatment for patients with PH and Heart Failure (HF). Studies using therapies targeted at the pulmonary vasculature in patients with HF have not yielded positive results. [3] [4, 5]

Sacubitril/valsartan (S/V), the first-in-class angiotensin receptor neprilysin inhibitor (ARNI), is the first drug to demonstrate a mortality benefit in patients with chronic heart failure and reduced ejection fraction. In the PARADIGM-HF trial [1] , patients with HFrEF treated with sacubitril/valsartan had a 20% reduction in the primary composite endpoint of cardiovascular death or heart failure hospitalization, compared with subjects receiving enalapril. The effects on cardiac volume and function were investigated in the *PROVE-HF*[6] and *EVALUATE-HF* trials [7], which showed improvements in selected echocardiographic endpoints, suggesting improvement in cardiac remodeling and estimated filling pressures; however, the mechanisms are not clear.

Treatment with S/V increases the circulating levels of natriuretic peptides, which have been shown to facilitate natriuresis and vasodilation[8] . This study aims at assessing the impact of sacubitril/valsartan a drug approved for heart failure with reduced ejection fraction (HFrEF), on the elevated pulmonary artery pressures, as measured by echocardiography, in patients with severe heart failure and pulmonary hypertension.

Methods

In order to investigate the effects of S/V in congestive heart failure, we selected 40 consecutive patients (31 males, 9 females, mean age 64±19 years) in NYHA class II-III because they had left ventricular ejection fraction (LVEF) ≤35% at echocardiography. Etiology: 22 coronary heart disease (CHD), 3 Myocarditis, 15 Idiopathic Dilated Cardiomyopathy (IDCM). See Table 1.

Imaging was performed using a Philips IE33 and a 5.2-MHz transducer (Philips Medical Systems, Andover, MA). The echocardiographic parameters investigated were PAPs (derived from a tricuspid regurgitation flow value of <2.8 m/s), ACTpo (normal value <100 msec), PVR (using the equation: PVR = TRV/TVI rvot × 10+0.16) [9], inferior vena cava flow, diameter and inspiratory changes (normal value >18 mm with respiratory collapse <50%), and Doppler tissue imaging (DTI) of the tricuspid annulus, which were evaluated using a Phillips IE33 echocardiograph equipped with 2.5 and 3.5 MHz electronic transducers, harmonic imaging and DTI.

The six-minute walking test (6MWT) consists of walking along a 30-metre corridor for the longest distance possible in six minutes using a standard protocol; as the test is symptom-limited, the patients are allowed to stop and resume walking when they wish. Before and after the test, the patients' vital parameters were recorded, and patients completed a visual analogue scale (VAS) quantifying the degree of dyspnea. Oxygen saturation (SPO2, expressed as a percentage) and heart rate (HR, expressed as beats per minute [bpm]) were continuously monitored and recorded every 10 seconds from five minutes before the walk to five minutes after returning to baseline values, using a portable pulsometer (Model 920 M, Health dyne, Marietta, GA). To avoid the learning effect, a pause of 60 minutes was allowed between each test . [10]

Ethical Concerns

The study was prospectively designed, in compliance with the principles outlined in the Declaration of Helsinki, and was approved by the internal Ethical Committee. All patients gave their informed consent.

Statistical analysis

All data are given as mean values ± SD, unless otherwise stated. Pearson's correlation coefficient and Bland-Altman analysis were used. The null hypothesis was rejected when p was ≤.05

Results

The baseline characteristics of our cohort are shown in Table 1. Out of 40 patients, 31 (77.5%) were males and 9 (22.5%) were females.

Mean age was 64±19 years. Upon enrolment, all patients had NYHA class II (n=17, 42.5%) or III (n=23, 57.5%); with regard to the left ventricular function assessment, the mean LVEF was 29.7±4.5%. CHD (n=22, 55%) was the most common etiology of HFrEF in our patients.

Upon the initiation of the S/V therapy, 38 patients (95%) received a dose of 24/26 mg/bid. After a median time of 3 months, the maximum S/V dose received was 97/103 mg/bid in 2 patients (5%), 49/51 mg/bid in 25 patients (62.5%) and 24/26 mg/bid in 13 patients (32.5%). Among the patients who did not reach the target dose of one 97/103 mg tablet twice daily, the main reason was symptomatic hypotension (n=11), while only a minority of patients (n=2) stopped the treatment due to kidney dysfunction and hyperkalemia.

During a mean follow-up of 24±6 months, no patients died. Implantable Cardioverter-Defibrillator implantation (ICD) was performed in 20 patients (50%).

The main findings of our study are shown in Table 2.

Discussion

The development of PH in patients with LHD is associated with poor prognosis.

The lack of recommendations concerning the use of PAH-specific therapies in patients with PH-LHD reflects the currently unclear data. Preliminary data suggest that intermittent PGE1 infusion in patients with advanced congestive heart failure and high pulmonary pressure is able to improve NYHA mean class, ventricular contractility, pulmonary pressure and clinical data. [11]

In our study, sacubitril-valsartan was able to improve NYHA class, 6MWT and PASP, even with only a slight improvement of the left ventricular ejection.

These data therefore confirm our hypothesis that S/V works through mechanisms involving also the pulmonary circulation.

The therapeutic strategy for heart failure has gradually evolved over the course of time. Different molecules, such as diuretics, ACE-inhibitors, beta-blockers and the antagonists of the mineralocorticoid receptors, showed a significant decrease in mortality in this condition, and established themselves as a reference treatment.

Among the new therapeutic strategies, natriuretic peptides with an antagonistic action on SRAA have favorable hemodynamics effects: they promote vasodilation, increase diuresis, glomerular filtration and renal blood flow, inhibit the release of renin and aldosterone and decrease sympathetic activity. [3,6]

Chronic elevation of the left-sided filling pressure may result in pulmonary arterial endothelial dysfunction, decreased nitric oxide availability, increased expression of endothelin-1, upregulation of neurohormones and vascular remodeling, leading to an increase in pulmonary artery pressures (PAP). [7] Sacubitril increases circulating NPs levels by inhibiting their breakdown by neprilysin. The beneficial

effects of NPs occur through a complex signaling system that involves the up-regulation of intracellular cyclic guanosine monophosphate, which induces direct vasodilation . Richard T. Clements and colleagues, using an animal model of PH, report that treatment with S/V for 6 weeks determines the regression of hypertrophy of the right ventricle. They also demonstrated that such improvements were associated with a reduction in pulmonary vascular remodeling, an improvement of the systolic function of the right ventricle and a reduction in the collagen content. [7,8,12]

Recently, however, Zubair Khan and colleagues showed that S/V could cause an acute reduction in mean pulmonary artery pressures after initiation, without an incremental reduction in after-dose increase and short-term follow-up.[13] The PARENT (Pulmonary Artery Pressure Reduction with Entresto) pilot trial aims at assessing the impact on an elevated pulmonary artery pressure in patients with reduced ejection fraction, measured using a previously implanted monitoring device (CardioMEMS). However, this study did not provide significant data, due to the lack of patients enrolled[14] .

S/V seems to improve the outcomes in patients with pulmonary hypertension associated to left heart disease (PH-LHD). [15] According to the data from the PARAGON-HF echocardiography sub-study, right ventricular enlargement and elevated left- and right-sided pressures were among the predictors of HF hospitalization or CV death among patients with HF with preserved ejection fraction; patients with indicators of pulmonary hypertension also had elevated risk for CV events. [16]

Our study confirms these effects of S/V on pulmonary circulation in patient with Heart Failure and reduced Left Ventricular Ejection Fraction (HFrEF): this can occur either through a reduction in the left ventricular telediastolic pressure or through an endothelial vasodilating action.

Conclusion

These preliminary data suggest that in patients with advanced congestive heart failure, S/V is able to improve NYHA class, 6MWT and PASP, even with only a slight improvement of ventricular contractility. The drug hasn't been associated with morbid events or an increased risk of death. Although the precise mechanisms responsible for the benefit in heart failure remain unclear, S/V may reduce the fluid retention and pulmonary vasoconstriction that contribute to heart failure symptoms.

Limitation

This data should be confirmed through studies involving a larger group of patients and using hemodynamic data from a right heart catheterization.

List of Abbreviation

S/V = sacubitril/valsartan

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF: Heart failure with reduced ejection fraction

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

NT-proBNP = N-terminal pro–brain natriuretic peptide

NYHA = New York Heart Association

PA = pulmonary artery

PASP = pulmonary artery systolic pressure

RV = right ventricular

TAPSE = tricuspid annular plane systolic excursion

TDI = tissue Doppler imaging

TR = tricuspid regurgitation

PH = Pulmonary Hypertension

LHD = Left Heart Disease

NPS = neprylisin

6MWT = six-minute walking test

VAS = visual analogue scale

SPO2 = Oxygen saturation

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table 1. Baseline characteristics of S/V population	
	n = 40
Age	64 ± 19
Sex	
Male	31 (77.5)
Female	9 (22.5)
NYHA functional class	
II	17 (42.5)
III	23 (57.5)
HFrEF etiology	
Ischemicv heart disease	22 (55)
Idiopathic dilated cardiomyopathy	14 (35)
Myocarditis	3 (7.5)

Hypertrophic cardiomyopathy	1 (2.5)
Baseline laboratory results	
EGFR, ml/min/1.73 m²	75 ± 26
BPN, pg/ml*	324
Serum potassium, mEq/L	4.4 ± 0.4
Other parameters	
Systolic blood pressure, mmHg	119 ± 12
Diastolic blood pressure, mmHg	75 ± 6
LVEF, %	29.7 ± 4.5
SPAP, mmHg	44 ± 12
6MWT, m	389 ± 108

Values are n (%) or mean ± SD or median(*). **NYHA**: New York Heart Association; **HFrEF**: Heart Failure with Reduced Ejection Fraction. **eGFR**: Estimated Glomerular Filtration Rate; **BNP**: Brain natriuretic peptide; **LVEF**: left ventricular ejection fraction. **SPAP**: systolic pulmonary artery pressure; **6MWT**: six minutes walking test.

Table 2. Results	
✓ **SPAP** decrease from **44.10 mm/Hg** + ES 2.2 DS 12.1 to **38.6 mm/Hg** + ES 1.87 DS 10.6	**p<0.05**
✓ **6MWT** improve from **389.83 meter** + ES 22.5 DS 108.1 to 6MWT **438 meter** + ES 22.5 DS 108.1	**p<0.05**
✓ **LVEF** improve from **29.7** % + ES 0.9 DS 4.5 to **33.4 %+** ES 1.1 DS 5.3	**p< 0.05**
✓ **NYHA** improve from **2.5** + SE 0.1 DS 0.5 to **2.0** + ES 0.1 DS 0.6	**p< 0.005**
T-test for paired data: there are no correlations between the parameters (PEARSON).	