

Sacubitril-Valsartan, a Promising Treatment for Heart Failure. First Clinical Experience

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Abstract

Heart Failure (HF) is a high prevalence disease whose incidence is increasing in the last decades. It supposes a progressive deterioration of the patient quality of life which often leads to death (50% of survival in 5 years). Frequent decompensations will also lead to hospitalization, with a high rate of readmissions (44% in the first year).

The knowledge of the physiopathology of HF and the neurohormonal systems that are involved in its such Renin-Angiotensin-Aldosterone and catecholamine systems, has allowed us to develop several pharmacological strategies which reduced significantly morbidity and mortality of HF (ACEI, ARAI, Beta blockers, MRAs).

The mechanism and biological effects of Natriuretic Peptides (NP) is also well known. Its clinical use has been tested in the last years and they are broadly established as biomarkers in diagnosis and prognosis in Heart Failure. A different approach has been recently achieved its use as therapeutic target.

The development of Sacubitril, an specific inhibitor of Neprilisin, the main enzyme in charge of degrading NP and therefore, its biological actions, in combination with Valsartan (Angiotensin Receptor Antagonist), has proved to be effective and safe in the treatment of patients with established HF with reduced Ejection Fraction.

The results of the clinical trial PARADIGM which compares the use of Enalapril (ACEI) with Sacubitril-Valsartan, showed an important reduction in the rate of cardiovascular death (20%), Hospitalization (20%), sudden death (20%) and death by any cause (16%) without significant side effects [4,5].

This is the reason for the modification of the new IC guidelines that includes Sacubitril-Valsartan as a treatment of HF (indication I B) in patients with PARADIGM profile (symptomatic HF, at least NYHA class II, Reduced EF, after Medical Optimal Treatment).

There are many analysis and sub analysis published with the results of PARADIGM, but its clinical experience is short. We would like to present a short cases series that confirms these results in real clinical practice.

Keywords: Sacubitril-Valsartan; Heart Failure; PARADIGM

Introduction

After the findings of the clinical trial PRADIGM, Sacubitril-Valsartan has emerged as an alternative therapeutic option with promising

results, and its use has been included in the new Guidelines for the management of Heart Failure of the European Society of Cardiology. Despite of these findings, the clinical experience is short. With this article, we would like to illustrate the initial management of the drug with a small case series.

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Case Report

Case 1

65-year-old man that underwent urgent cardiac surgery as a consequence of type A aortic dissection. In the echocardiogram performed he had normal EF, moderate hypertrophy, without other alterations. As other comorbidities he was ex-smoker, DM, dislipemia, peripheral arteriopathy and mild COPD. He presented a postquirurgic AV block and finally a pacemaker was implanted (VDD). After a good cardiovascular evolution, he was discharged with this treatment: telmisartan 40 mg, clopidogrel, simvastatin, levothyroxine, metformin.

In next months, he needed three new vascular surgical interventions that were performed without any cardiac problem. Six months after, he was admitted at hospital with breathless, swollen legs and other clinical and radiological HF signs and symptoms the new echocardiogram performed showed a moderate dilated Left Ventricle(LV) (edLVv 253 mL, edLVd 67 mm) global hypocinesy, LVEF 29%, moderate diastolic dysfunction, mild pulmonar hypertension. After that, he showed satisfactory clinical evolution after intravenous diuretic. MRAs were added; beta blockers were not tolerated.

The treatment at that moment was telmisartan 20 mg, furosemide 40 mg, espirolactone 25 mg Next months he must be hospitalized several times for HF. comorbidities (lung infection, anemia) were treated; up titration of furosemide was needed, and the patient was in NYHA class III. A coronary angioCT was performed but no severe stenosis were founded The pacemaker asynchrony pacing was assumed as the most probable etiology and upgrading to resynchronization (CRT) was performed. Little improvement in echocardiogram was observed (LVEF 32%) and also referred by patient and was established in functional class II-III. In remote monitoring, ventricular arrhythmias were found and amiodarone was started. We have a non ischaemic dilated cardiomyopathy with severe ventricular dysfunction, symptomatic, with frequent decompensations despite of Optimus Medical Treatment (OMT) including 6 months of CRT, with ventricular arrhythmias. He was found to be a perfect candidate for sacubitril-valsartan (matches all the parameters from PARADIGM trial) so a request for compassionate use was made and accepted (at that moment, the drug was not available in pharmacy) At medical office, without any additional control, telmisartan (ARAI) was directly substituted (without blanking period) for sacubitril-valsartan 24/26 BC. The patient was instructed to increase to 49/51 BC himself after 2 weeks. He suffered oligosymptomatic hypotension so higher dose was not reached until a month.

Two months after, the patient was stable at NYHA class II. Furosemide was reduced to 40mg daily. The echocardiogram performed showed a significant recovery of LVEF to 49% (previous 32%), with a volume reduction, and normalization of pulmonary pressure.

No more hospitalization for HF in the next 4 months and no more ventricular arrhythmias were documented.



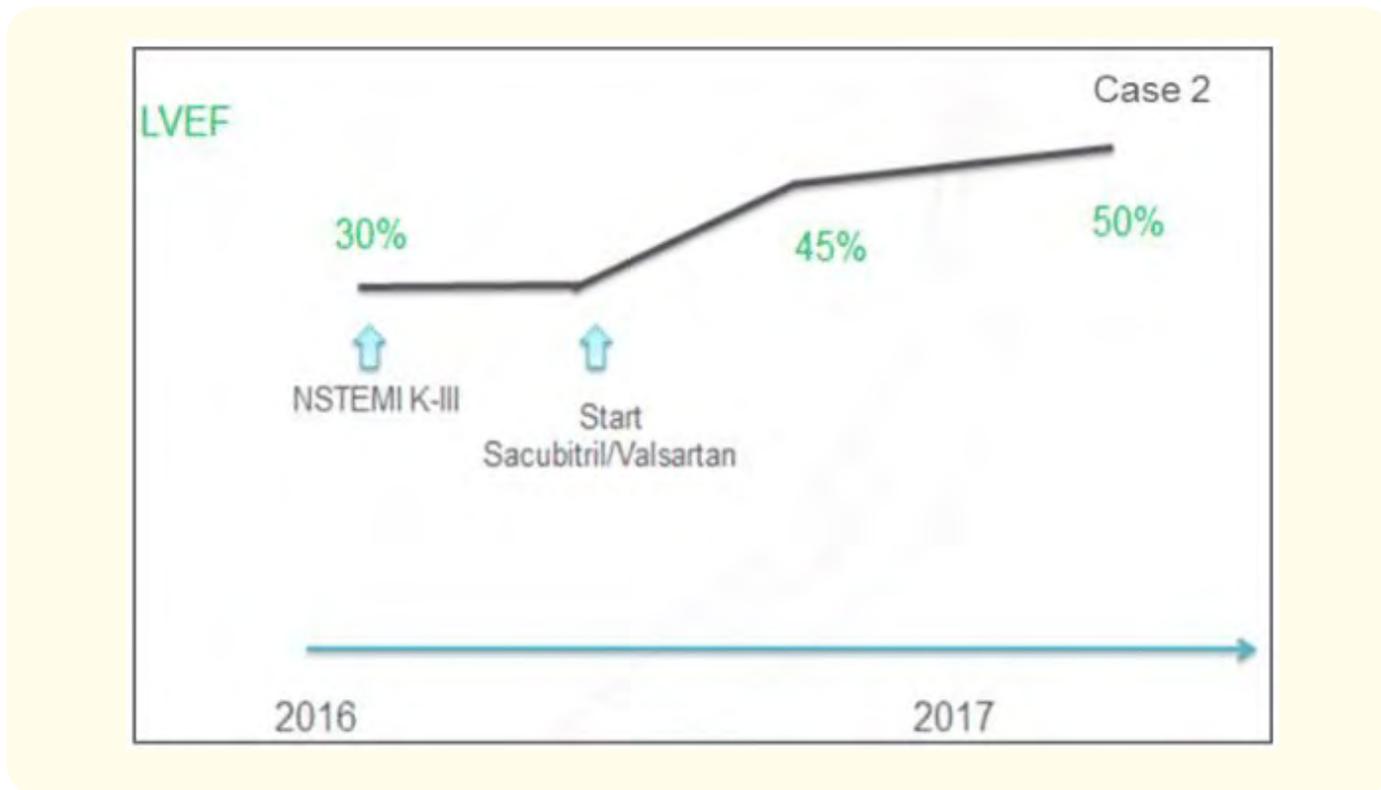
Case 2

82-year-old woman without relevant medical history (only treated esquizophrenia) was admitted at hospital with acute pulmonary edema and after stabilization in the Intensive Care unit an echocardiogram was performed. It showed anteroapical akinesia, inferior hypoquinesia, with a 30% LVEF and a moderate to severe ischemic mitral regurgitation. In coronariography 3 vessels disease and surgical revascularization was decided. However, after a new angina episode and in estabilization, an urgent PCI for Right coronary and circumflex was made. After a 45-days Hospitalization he was discharged with this treatment: aspirin, clopidogrel, carvedilol 6,25 BC, spironolactone 25, furosemide 40 mg, enalapril 5 mg/day.

After one month, she was reviewed at medical office. She was in NYHA Class III with orthopnea and mild effort dyspnea, and echocardiogram showed 35% LVEF.

With the diagnosis of Ischemic Dilated Cardiomyopathy, with severe Ventricular Dysfunction, Symptomatic despite OMT, Sacubitril-Valsartan was initiated. She had an arterial pressure of 140/80 mmHg, nevertheless small dose 24/26 BC was elected. As she was in treatment with ACEI (enalapril) 36h blanking period was performed. The patient was instructed to increase to 49/51 BC which was performed without supervision.

Four months after that, all signs of HF disappeared. She was in NYHA class I-II. In the echocardiogram performed, a moderate anterior hypoquinesia persisted, but LVEF had raised to 50%.



Case 3

87-year-old woman, followed in cardiology for an aortic biologic prosthetic valve with a LIMA to Left Anterior Descending (LAD) 5 years ago. She was stable in NYHA class I-II.

Her echocardiogram showed non-dilated VI with abnormal septal movement a light inferior hipoquinesia with a LVEF 49%; no other abnormalities including normal aortic prosthetic valve.

Treatment at that moment: aspirin, losartan, doxazosin, carvedilol, atorvastatin.

She was also with amiodarone treatment for symptomatic non-sustained ventricular tachycardias.

She was attended at medical office for rest breathless and a new echocardiogram was performed, finding global hipoquinesia with a severe Ventricular dysfunction (LVEF 23%).

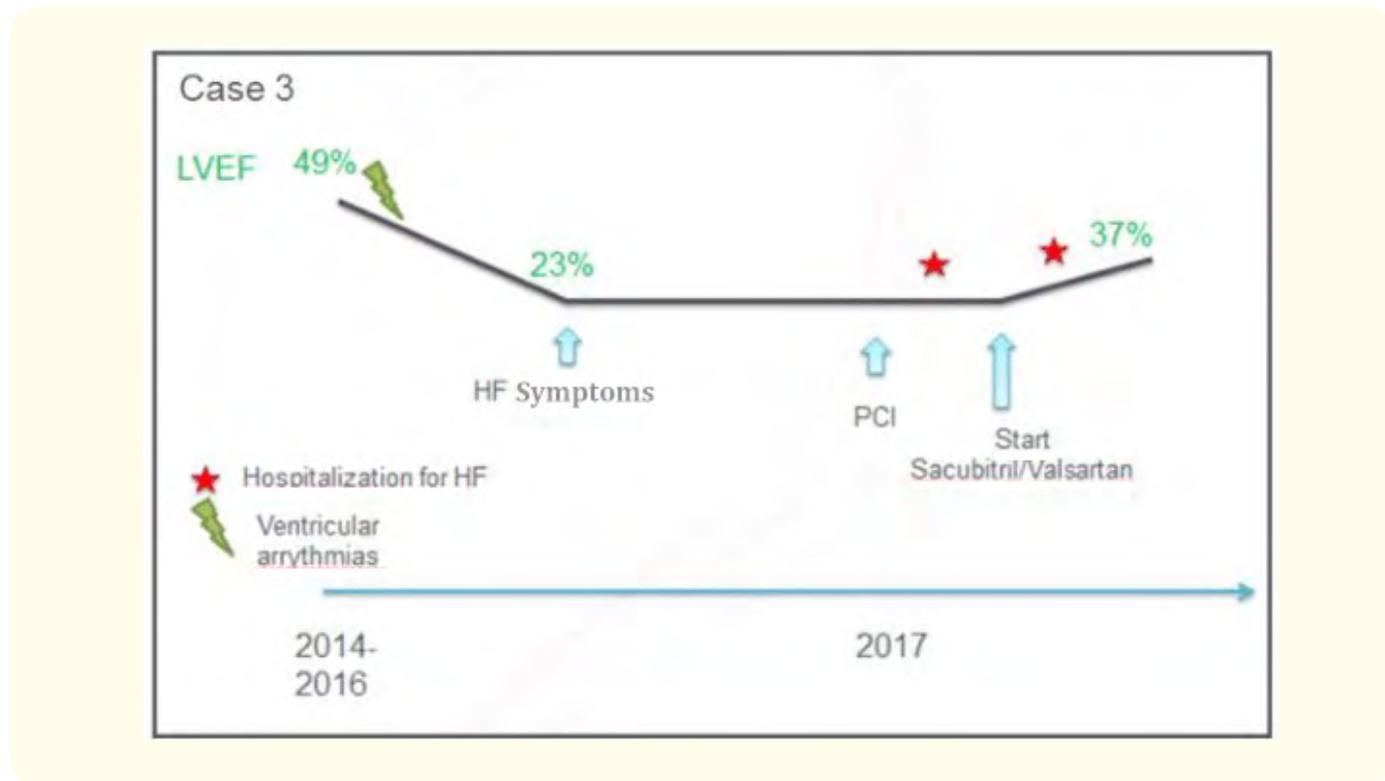
A coronariography showed LIMA to LAD permeable but severe obstruction in Right Coronary, so one Drug Eluting Stent was implanted.

However, 15 days after revascularization, the patient was admitted at hospital for progression in HF symptoms. After 15 days with high dose of furosemide, he was discharged. Last days at hospital, Sacubitril-Valsartan was initiated.

Treatment at that moment was furosemide 80 mg, carvedilol 6,25BC, sacubitril-Valsartan 24/26 BC, aspirin clopidogrel atorvastatin.

Two weeks after that, she was hospitalized for persisting symptoms but no further treatment changes were made. One month after that, a new echocardiogram was performed. It showed global hypoquinesia but, at this time, the LVEF had improved to 37%. The dose of Sacubitril Valsartan was increased to 49/51 BC.

Next three months, she was stable in NYHA class III.



Discussion

In all our patients, Sacubitril-Valsartan was initiated in the consultation without additional test and was up titrated by patients themselves without direct supervision. Only hypotension was reported as a secondary effect and did not led to drug withdrawal. The improvement in clinical condition and the echocardiogram parameters were shown strikingly early.

In all patients described, drug was started at the consultation, without any additional control. The patient was instructed in the up titration of the dose which was performed without direct supervision. Clinical improvement was reported from the first month and echocardiogram performed within first three months showed volume reduction and improvement of EF and diastolic function. Hypotension was the only side effect referred which did not lead to drug withdrawal but delayed reaching a higher dose.

Conclusion

Sacubitril-Valsartan is a new therapeutic option available in treatment of HF. Its clinical use is simple, safe and effective.

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