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SHORT COMMUNICATION

Sacubitril–valsartan in heart failure and multimorbidity patients

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Abstract

Aims The poor control of symptoms in patients with advanced heart failure with reduced ejection function (HFrEF) can limit the functionality of patients. Sacubitril–valsartan, compared with enalapril, has been shown to reduce mortality and hospitalization, and nowadays, there is still little evidence about the improvement on functionality. The aim of our study is to analyse the improvement of the functional class and the 6 min walking test (6MWT) in patients with multiple pathologies and advanced heart failure.

Methods and results From September 2016 to March 2018, 65 multimorbidity patients with severe symptomatic HFrEF were initiated to receive sacubitril–valsartan. Mean age was 78.6 ± 7.4 years, and 68% were male. The Charlson co-morbidity index was 8 points. Seventy-four per cent had New York Heart Association (NYHA) Functional Class IV. After the treatment, patients were able to achieve 55.68 m or more on 6MWT, and 91% presented an improvement in the NYHA functional class.

Conclusions Sacubitril–valsartan relieves symptoms and improves functional class prognostic risk of patients with advanced HFrEF and co-morbidity.

Keywords Sacubitril–valsartan; Elderly; Multimorbidity; Six-minute walking test; NYHA; MAGGIC score

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Introduction

Heart failure (HF) is a progressive illness that is highly prevalent among the elderly. Multimorbidity, defined as the co-occurrence of two or more chronic conditions, is a common condition in adults, and the prevalence increases with age.[1] Multimorbidity increases the risk of adverse outcomes such as declining functional status, hospitalizations, and death,[1] the same as HF.[2,3] There is important recognition to consider co-morbidity in treatment decision because co-morbidity in multimorbidity patients with HF may worsen its management and prognosis.[4]

The PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial[5] showed that sacubitril–valsartan reduced the risk of cardiovascular death or first hospitalization for HF. But there is little evidence regarding the study of the functionality of patients after treatment,[6,7] and there is little evidence of the drug in elderly patients with multimorbidity.[8]

The aim of this study is to evaluate if the use of sacubitril–valsartan improves functionality in multimorbidity patients with HF and the factors and prognostic tests in elderly patients with advanced HF and multimorbidity.

Methods

Study population

In this observational study, we included all HF with reduced ejection function (HFrEF) patients assessed in the Chronic-Multimorbidity Unit of the Complejo Hospitalario de Navarra in the period from September 2016 to March 2018.

The Chronic-Multimorbidity Unit performs the assessment and monitoring of patients with two or more chronic medical conditions (ischaemic cardiomyopathy, diabetes, chronic kidney disease, HF, chronic obstructive pulmonary disease, dementia).

We included patients with HFrEF diagnosis in based on the guidelines of European Society of Cardiology on 2016 and who had dyspnoea at rest or with minimal or slight limitation on physical activity.

The clinical history data were acquired in relation to the data obtained in the usual medical visit of each patient. Follow-up clinical visits were made on the basis of the clinical evolution of the patient.

Complete medical history with clinical variables (blood pressure, medication, results of echocardiography), laboratory values (creatinine, albumin, glycosylated haemoglobin [HbA1c], troponin T, brain natriuretic peptide levels), Barthel index, and 6 min walking test (6MWT) was obtained at the beginning and end of the study period. The New York Heart Association (NYHA) scale assessment was performed in each of the consultations made throughout the follow-up. The MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) score was calculated in the first consultation and prior to the analysis of the study. We compared all of these variables before and after sacubitril–valsartan treatment.

All patients provided informed consent, and the protocol was approved by the research ethics committee in accordance with the principles of the Declaration of Helsinki and national regulations.

Statistical analysis

Normally distributed continuous variables are reported as means with standard deviations and non-normally distributed continuous variables as medians. Categorical variables are summarized as frequencies and percentages and were compared using χ^2. We analysed before and after group differences using Student's *t*-test for continuous variables and χ^2 test for categorical values. We considered a *P*-value < 0.05 to be statistically significant. We performed all analyses with STATA, Version 12.0 (Texas).

Results

Between September 2016 and March 2018, 65 patients with HFrEF (left ventricular ejection fraction mean was 37%) severely symptomatic were initiated to sacubitril–valsartan treatment and were followed up by the Chronic-Multimorbidity Unit. The mean age was 78.6 ± 7.4 years, and 68% of the patients were male. The median Charlson co-morbidity index was 8 points. Chronic kidney disease was the most common co-morbidity (86%), presenting in 58% of patients with moderate/severe kidney disease. The most common aetiology of HFrEF was ischaemia (52%); 66% of the patients received previous treatment with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 98% received diuretic treatment. Patients' basal characteristics are described in *Table 1*.

Treatment with sacubitril–valsartan was well tolerated without side effects. The mean treatment time was 286 days. Seventy-five per cent of patients received the maximum dose of 24/26 mg every 12 h.

There was a significant difference of 55.68 m or more in the 6MWT after initiating sacubitril–valsartan (223.44 vs. 279.12, $P < 0.001$, 95% CI 74.26–27.07) (*Table 2*).

Prior to the start of the drug treatment, most of the patients had NYHA IV (74%), followed by NYHA III (25%); at the end of the study, an improvement of NYHA was observed, being most frequently NYHA II and III (51% and 40%, $P = 0.002$) (*Table 2*).

There were no statistically significant differences between the mean values of the MAGGIC score (38.14 vs. 28.75). Patients were classified according to the six risk groups of the

Table 1 Baseline characteristics of patients prior to the start of sacubitril–valsartan

Characteristics[a]	*n* = 65
Age, years	78.6 ± 7.4
Sex (M/F)	44/21
BMI (kg/m^2)	29.4 ± 5.6
Mortality, *n* (%)	13 (20)
Charlson co-morbidity index	8
Barthel index	80
Clinical features of heart failure	
Left ventricular ejection fraction (%, SD)	37 ± 2.3
Pulmonary blood pressure (mmHg)	46.1 ± 16.1
Aetiology of heart failure, *n* (%)	
Hypertensive	14 (22)
Ischaemic	34 (52)
Valvular	8 (12)
Mix of ischaemic/valvular	9 (14)
Medical history, *n* (%)	
Hypertension	39 (65)
Diabetes	44 (68)
Atrial fibrillation	46 (71)
Myocardial infarction	34 (52)
COPD	21 (32)
Chronic kidney disease, *n* (%)	56 (86)
Stage 2	8 (12)
Stage 3a	19 (29)
Stage 3b	21 (32)
Stage 4	17 (26)
Treatment, *n* (%)	
Pre-use ACE-I or ARB	43 (66)
Beta-blocker	48 (74)
Mineralocorticoid agonist	28 (43)
Diuretic	61 (98)
Digitalis	18 (28)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range.
[a]Plus–minus values are means ± SD.

Table 2 Comparison of the analytical and clinical characteristics before and after the start of sacubitril–valsartan

Characteristics[a]	Before	After	*P*
Clinical			
Blood pressure (mmHg)	125.8 ± 18.8	127.7 ± 21.7	0.43
6 min walking test (m)	223.44 ± 93.55	279.12 ± 104.81	<0.001
NYHA scale, *n* (%)			0.002
Class II	1 (1)	33 (51)	
Class III	16 (25)	26 (40)	
Class IV	48 (74)	6 (9)	
MAGGIC score, *n* (%)	38.14	28.75	<0.001
MAGGIC score Risk Group 1	1 (1)	2 (3)	
MAGGIC score Risk Group 2	1 (1)	3 (4)	
MAGGIC score Risk Group 3	1 (1)	9 (14)	
MAGGIC score Risk Group 4	11 (16)	17 (26)	
MAGGIC score Risk Group 5	13 (20)	16 (25)	
MAGGIC score Risk Group 6	38 (61)	18 (28)	
Treatment (mg/dL)			
Mineralocorticoid agonist	29.01	26.34	
Diuretic	78.77	96.62	
Analytics			
Serum creatinine (mg/dL)	1.62 ± 0.58	1.66 ± 0.58	0.53
Serum troponin T (pg/mL)	45.07 ± 48.17	36.22 ± 30.45	0.03
Serum HbA1c (%)	7.18 ± 1.7	7.04 ± 1.6	0.83
Serum albumin (mg/dL)	3.89 ± 0.43	3.87 ± 0.36	0.44
Serum BNP (pg/mL)	565.5 ± 579.49	654.21 ± 1292.2	0.36

BNP, brain natriuretic peptide.
[a]Plus–minus values are means ± SD.

MAGGIC score. Prior to the treatment, 61% of patients were in Group 6 risk, followed by 20% in Group 5. After sacubitril–valsartan treatment, we observed a redistribution of patients between Groups 3, 4, 5, and 6 (14%, 26%, 25%, and 28%, respectively; $P < 0.001$) (*Table 2*).

On the analytical values, we found statistically significant differences in troponin level reduction (45.07 vs. 36.22, $P = 0.03$). There were no statistically significant differences between creatinine, albumin, and HbA1c levels. There were also no differences between blood pressure levels (*Table 2*).

Discussion

In our population, sacubitril–valsartan is a major breakthrough in HF treatment because it has shown benefit on functionality and risk reduction in patients with HFrEF in advanced functional class and multimorbidity.

The implication of different mechanisms of sacubitril–valsartan in the improvement of exercise capacity has been postulated (effect of natriuretic peptides, inhibition of neprilysin, modulation of endorphin–enkephalin system), but the effect of the same remains unclear yet.In recent studies, sacubitril–valsartan improves the functionality of patients through the improvement of domestic activities.[7] Similar studies show an improvement in the distance travelled in the 6MWT.[6] However, the main difference in these studies is that up to 50% of patients had advanced functional class (NYHA III/IV), unlike in our population, in which our entire study population presented with an advanced functional class. Moreover, 75% of patients only reached the maximum dose of 24/26 mg every 12 h, similar to the results found in the literature.[6]

It is interesting to note that the clinical benefit observed in our population despite age, concordant with sacubitril–valsartan, when compared with enalapril, in the study PARADIGM-HF, was consistent in patients > 75 years.[8]

In our population, we have observed a decrease in the MAGGIC score after the start of the drug, which is equivalent to a decrease in the risk of cardiovascular death, as was shown in the PARADIGM-HF study regarding patients on treatment with enalapril.[9]

Having no control group and the limited number of patients can be some of the limitations of this study. Sacubitril–valsartan, in real life, can help in the correct management of patients with HFrEF and co-morbidity, even in advanced stages of the disease, as well as improve the functionality and therefore the quality of life of our patients, also improving the prognosis, not simply with the goal of increasing the longevity of patients.

Conflict of interest

None declared.

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