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Original article

Initiation and titration of sacubitril/valsartan in different types of centers

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ABSTRACT

Introduction and objectives: Sacubitril/valsartan (SV) is recommended in patients with heart failure and reduced left ventricular ejection fraction. However, the characteristics of the centers included in the pivotal clinical trial differ from real life. The present study aims to analyze the clinical profile of patients treated with SV according to hospital type and the potential role of these differences in drug safety and effectivity.

Methods: Prospective multicenter registry that included outpatients treated with SV. We compared baseline characteristics and treatments, drug titration, and data at 7-months follow-up according to hospital type.

Results: From 427 patients, 81 (19%) were included in medium/small size hospitals, 204 (48%) in heart transplant program centers and 142 (33%) in hospitals with ≥1000 beds without heart transplant program. A low starting dose of SV (50 mg bid) was more frequent in medium/small size hospitals than in hospitals with ≥1000 beds (51 [63.0%] vs 151 [43.6%] patients, $P = .008$). At 7 months, SV had been withdrawn more frequently in medium/small size hospitals than in hospitals ≥1000 beds (15 [18.5%] vs 34 [9.8%] patients, $P = .001$], in spite of a similar rate of adverse events (23 [28.4%)] vs 99 [28.6%] patients, $P = .94$).

Abbreviation: SV: sacubitril/valsartan.

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Conclusion: In our registry, the use of SV in real life showed a low rate of events during follow-up. The above suggests that this drug is safe and beneficial in different clinical profiles of patients but drug withdrawal is more frequent in medium/small size hospitals.

Inicio y dosificación del sacubitrilo-valsartán en diferentes tipos de centros

Palabras clave:
Sacubitril/valsartán
Insuficiencia cardíaca
Tipo de hospital

RESUMEN

Introducción y objetivos: Se recomienda el sacubitrilo-valstartán (SV) en pacientes con insuficiencia cardiaca y fracción de eyección reducida. Sin embargo, las características de los centros incluidos en los ensayos clínicos fundamentales son diferentes a las de los centros en la vida real. El objetivo del presente estudio fue analizar el perfil clínico de los pacientes tratados con SV según el tipo de hospital y el papel potencial de estas diferencias en la seguridad y la efectividad de este fármaco.
Métodos: Registro multicéntrico prospectivo que incluyó a pacientes ambulatorios tratados con SV. Se compararon las características basales y los tratamientos, la dosificación del fármaco y los datos a los 7 meses de seguimiento.
Resultados: De 427 pacientes, 81 (19,0%) se incluyeron en hospitales de tamaño medio/pequeño, 204 (48%) en centros con programa de trasplante cardiaco y 142 (33%) en hospitales con ≥ 1.000 camas sin trasplante cardiaco. Una dosis de inicio baja de SV fue más frecuente en hospitales de tamaño medio/pequeño que en hospitales con ≥ 1.000 camas (51 [63,0%] frente a 151 [43,6%] pacientes, p = 0,008). A los 7 meses, el SV se había retirado con mayor frecuencia en hospitales de tamaño medio/pequeño que en hospitales ≥ 1.000 camas (15 [18,5%] frente a 34 [9,8%] pacientes, p = 0,001], a pesar de una tasa similar de eventos adversos (23 [28,4%)] frente a 99 [28,6%] pacientes, p = 0,94).
Conclusión: En nuestro estudio, el uso de SV en la vida real mostró una tasa baja de eventos en el seguimiento. Esto sugiere que este fármaco es seguro y beneficioso en diferentes perfiles clínicos de pacientes, si bien el fármaco se suspendió con mayor frecuencia en los hospitales de tamaño medio/pequeño.

Introduction

Heart failure is a complex clinical syndrome and a serious public health problem due to its high prevalence and poor prognosis.[1–4] It is a frequent cause of hospital admission and resources consumption.[5,6] The PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure)[7] was a recent milestone in the pharmacological therapy of heart failure with reduced left ventricular ejection fraction.[8] This trail showed that, in symptomatic patients, sacubitril/valsartan (SV) achieved a greater reduction in cardiovascular mortality and heart failure admissions than enalapril. For this reason, the switch from angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers to SV is now recommended in clinical practice guidelines in symptomatic patients that present heart failure with reduced ejection fraction.[9,10] Recently an expert consensus has been published indicating that the initiation of SV may be considered for naïve patients hospitalized.[11] Despite these results, the characteristics of patients included in clinical trials are frequently different from real life.[12] The present study aims to analyze the clinical profile of patients treated with SV according to hospital type. We also studied the potential role of these differences and of hospital characteristics in drug safety and effectivity.

Methods

We performed a multicenter and prospective registry including all adults that received SV as outpatients and accepted the participation in the study in 10 hospitals from Madrid (Spain). This study was carried out between October 1, 2016 (date of commercialization of SV in Spain) and March 31, 2017. The recruitment was performed sequentially. The exclusion criteria were as follows: a) SV initiation during hospital admission and b) refusing to sign the informed consent. Patients were monitored in routine visits or with scheduled telephone visits during the follow-up period (7.0 ± 0.1 months). There were no patient losses.

Assessed variables included demographic and clinical characteristics, heart failure treatment, laboratory results, left ventricular ejection fraction, variables related to SV

Table 1 – Baseline characteristics and heart failure treatment according to hospital type.

	Heart transplant (*n* = 204)	≥1000 beds, no heart transplant (*n* = 142)	Medium/small-size (*n* = 81)	*P*
Age (years) mean ± SD	64.1 ± 11.7	72.4 ± 12.9	67.8 ± 10.2	<.001
LEVF	28.9 ± 7.1	29.7 ± 6.6	27.1 ± 6.9	.83
SBP (mmHg)	118.0 ± 4.2	123.0 ± 4.3	123.0 ± 4.3	.027
NT-ProBNP (pg/mL)	2548 ± 51	4536 ± 78	3147 ± 63	.001
Glomerular filtration rate (mL/min)	60.3 ± 4.5	60.7 ± 4.7	61.4 ± 4.5	.954
Potassium (mEq/L)	4.61 ± 0.5	4.44 ± 0.5	4.57 ± 0.4	.006
			Functionalclass	0.004
I	2 (1.0)	1 (0.7)	2 (2.5)	
II	124 (61.1)	109 (76.8)	59 (72.8)	
III	64 (31.5)	31 (21.8)	20 (24.7)	
IV	13 (6.4)	1 (0.7)	0	
High ACE inhibitor/ARB dose	187 (91.7)	81 (57.0)	69 (86.3)	<.001
Betablockers	193 (94.6)	134 (94.4)	76 (93.8)	.694
MRA	171 (83.8)	94 (66.2)	60 (74.0)	<.001
ICD	146 (71.6)	52 (36.6)	31 (38.2)	<.001
CRT	63 (30.9)	35 (24.6)	11 (13.6)	<.001

ACE, angiotensin convertor enzyme; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LEVF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-ProBNP, N-terminal pro-B-type natriuretic peptide, SBP, systolic blood pressure, SD, standard deviation.
Data are expressed as no. (%), mean ± standard deviation.

(discontinuation rate, initial dose, and dose at the end of follow-up), vital status, and hospital readmissions during follow-up. Baseline characteristics and treatments, drug titration and data at 7 months follow-up were compared according to hospital type.

Hospitals in the registry were grouped as follows: 3 centers with heart transplant program that included 204 patients, 2 hospitals with ≥1000 beds without heart transplant program that included 142 patients, and 5 medium/small-sized hospitals that included 81 patients.

This study was carried out in accordance with the recommendations of the Declaration of Helsinki and the principles of good clinical practice. All subjects gave written informed consent. The protocol was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañon, Madrid, Spain.

Statistical methods

Categorical data are shown as frequencies/percentages and were compared with the Chi-square test and the Fischer exact test. Continuous variables are summarized using the mean ± standard deviation or as the median and interquartile range if they do not follow the normal distribution determined by the Kolmogorov–Smirnov goodness-of-fit test. Continuous variables were compared with ANOVA for the comparison of means or the Wilcoxon rank sum in non-parametric data. The analysis of independent predictors of SV starting dose, performed using a logistic regression model has been previously published[13] and showed an independent association with the type of center. The regression model used an inclusion *P threshold* < .05 and an exclusion *P threshold* > .1. For all statistical analysis, Stata package version 14.0 (Stata Corp, College Station, United States) was used.

Results

A total of 427 outpatients were recruited during the inclusion period. In 346 patients (81.0%) SV was initiated in hospitals with ≥ 1000 beds (204 in centers with heart transplant program and 142 in centers without heart transplant program) and in 81 patients (19.0%) in medium/small size hospitals.

The baseline characteristics and the heart failure treatment according to hospital type are summarized in Table 1. Significant differences were found in mean age, systolic blood pressure, potassium levels, N-terminal pro-B-type natriuretic peptide levels at the time of inclusion, and functional class. We also found some differences regarding previous medical treatment and devices. The prevalence of cardiac devices carriers was lower in medium/small hospitals than in hospitals with ≥1000 beds (31 [38.2%} vs 198 [57.2%] patients with implanted cardioverter defibrillator, *P* < .001; 11 [13.6%] vs 98 [28.3%] patients with cardiac resynchronization therapy, *P* < .001).

Table 2 shows the initial dose of SV, dose changes, dose at the end of the follow-up, and SV withdrawal. A low starting dose of SV (50 mg bid) was more frequent in medium/small size hospitals than in hospitals with ≥1000 beds (51 [63.0%] vs 151 [43.6%] patients, *P* = .008). At 7 months, SV had been withdrawn more frequently in medium/small size hospitals than in hospitals ≥ 1000 (15 [18.5%] vs 34 [9.8%] patients, *P* = .001], in spite of a similar rate of adverse events (23 [28.4%] vs 99 [28.6%] patients, *P* = .94).

Hospital type was an independent predictor of starting SV at a high dose (100 or 200 mg bid). Hospitals with heart transplant [odds ratio (OR) 1], hospitals with ≥1000 beds, no heart transplant (OR, 0.78; 95% confidence interval [95%CI], 0.45–1.39; *P* = .411), and medium/small size hospitals (OR, 0.33; 95%CI, 0.18–0.61; *P* < .001).

Table 2 – Titration of sacubitril/valsartan according to hospital type.

	Heart transplant (*n* = 204)	≥1000 beds, no heart transplant (*n* = 142)	Medium/small size (*n* = 81)	*P*
Starting dose[a]				<.001
Low	74 (36.3)	77 (54.2)	51 (63.0)	
High	130 (63.7)	55 (38.7)	30 (37.0)	
Dose changes during follow-up				<.0001
No changes	60 (34.3)	79 (57.7)	19 (28.8)	
Dose increase	99 (56.6)	48 (35.0)	45 (68.2)	
Dose decrease	16 (9.1)	10 (7.3)	2 (3.0)	
Dose at the end of follow-up (twice daily)				.0001
50 mg	22 (12.6)	57 (41.6)	14 (21.2)	
100 mg	61 (34.8)	62 (45.3)	19 (28.8)	
200 mg	92 (52.6)	18 (12.4)	33 (50.0)	
SV withdrawal	29 (14.2)	5 (3.5)	15 (18.5)	.001

SV, Sacubitril/valsartan.

[a] Low dose (50 mg twice a day) and high dose (100 or 200 mg twice a day).
Data are expressed as no. (%).

Table 3 shows the events during follow-up. Medium/small-sized hospitals had the highest number of hospital admissions, without other significant differences. Most patients were in functional class I at the end of follow-up.

Discussion

The main finding of our study was that the use of SV is safe and beneficial in different profiles of patients in real life, although medium/small size hospitals use low doses more frequently and have a higher rate of drug withdrawal than bigger centers.

Despite the euphoria generated by the results of the PARADIGM-HF trial,[7] there were several unresolved issues,[14] especially regarding safety, since the patient profile in real life is different from the profile seen in randomized clinical trials.[15,16] In fact, in a previous work it was shown that in every-day clinical practice, SV is used more frequently in elderly patients with poor functional class.[13]

In hospitals with ≥ 1000 beds without a heart transplant program, older patients were included (72.4 ± 12.9 years), and this could explain higher levels of N-terminal pro-B-type natriuretic peptide, lower rate of patients with a high angiotensin-converting enzyme inhibitors/angiotensin receptor blocker dose and lower percentage of mineralocorticoid receptor antagonists. This may be the reason that in this type of centers, a low starting dose of SV was used more frequently than in centers with a heart transplant program. This could justify a lower need to reduce the dose and SV withdrawal at the end of the follow-up.

We found a greater number of hospital admissions in medium/small-sized hospitals compared to the rest; however the overall 6-months mortality can be considered low (12 deaths [2.8%]), without significant differences among the

Table 3 – Events during follow-up.

	Heart transplant (*n* = 204)	≥ 1000 beds, no heart transplant (*n* = 142)	Medium/small-sized hospitals (*n* = 81)	*P*
Hospital admissions	35 (17.7)	14 (9.8)	19 (23.5)	.021
Adverse effects				.911
Symptomatic hypotension	30 (14.8)	31 (21.8)	9 (11.1)	
Renal failure	16 (7.4)	7 (4.9)	8 (9.8)	
Hyperkalemia	13 (6.5)	2 (1.4)	6 (7.4)	
All-cause death	6 (2.9)	6 (4.2)	0	.063
Functional class at the end of follow-up				<.001
I	96 (47.0)	132 (93.0)	59 (72.8)	
II	76 (37.3)	7 (4.9)	19 (23.4)	
III	26 (12.7)	2 (1.4)	3 (3.8)	
IV	6 (3.1)	1 (0.7)	0	
Functional class > II at the end of follow-up	32 (15.8)	3 (2.1)	3 (3.7)	<.001

Data are expressed as no. (%).

groups. Medium/small size hospitals had also the highest rate of SV withdrawal (19%), as it has previously been shown that this withdrawal is associated with a poor prognosis,[17] this could be a matter of concern. At 7 months, SV was removed more frequently in medium/small hospitals than in hospitals with ≥1000 beds. We must emphasize that our study began in the first 6 months of commercialization of SV in our country (when clinical experience was scarce), added to the fact that the largest hospitals have greater and better resources (heart failure units) that allow closer monitoring of the patient. This could explain the higher percentage of SV withdrawal in medium/small size hospitals. It is important to point out that no patient from medium/small hospitals died during follow-up and that only 3 (4%) had a functional class > II at the end of follow-up. So, although our data are not enough to show an independence of the type of hospital with SV withdrawal, the larger SV removal does not seem to be related with a worse clinical situation. We found a higher admission rate in heart transplant centers than in large hospitals without heart transplant program, probably related to a more complex profile and a more advanced functional class.

At the end of the follow-up, the proportion of patients in functional class > II was low in all hospitals. Taking into account that in our study there was a high percentage of patients with a baseline poor functional class, as well as a worse clinical profile than in the pivotal trial, our results suggest that SV in real life is effective in different patient profiles and in different hospital settings.

Regarding safety, symptomatic hypotension was frequent, but we did not find relevant differences among different hospital types regarding the rate of adverse events, confirming the safety of the drug in all types of centers.

Hospital type was an independent predictor of starting SV at a high dose. A high SV dose was more frequently used in hospitals with heart transplant programs, and this fact probably explains their higher downtitration rate seen during follow-up. Medium/small hospitals were those that started SV at a lower dose.

Centers ≥ 1000 beds without heart transplant program had the lowest number of hospital admissions and the lowest rate of patients in functional class > 2 at the end of follow-up. Interestingly, these were the centers with the lowest SV discontinuation rate, in probable relation with a more frequent use of low doses, suggesting that it is often preferable to maintain a low SV dose than no dose at all.

Our study has some limitations related to its observational nature. The characteristics and profile of the population may not be generalizable to other geographical areas; in particular, the majority of our patients came from university hospitals that are reference centers in heart failure, which could be susceptible to selection bias.[18] This fact probably contributed to a good compliance with clinical practice guidelines. On the other hand, it is important to underline that our study is limited only to the Madrid region. Taking into account the heterogeneity of the health system between the different regions of Spain, our results may not be applicable to other health areas in the country. In addition, 7 months is a short follow-up period. Finally, our study gives important information regarding the use of SV in everyday clinical practice, a setting where information regarding this drug still is extremely scarce.[19–21]

Conclusions

In our registry, the use of SV in real life showed a low rate of events during follow-up. The above suggests that this drug is safe and beneficial in different clinical profiles of patients with heart failure and reduced left ventricular ejection fraction. Medium/small size hospitals use low doses more frequently and have a higher rate of drug withdrawal than high-volume centers.

What is known about the subject?

- Sacubitril/valsartan is recommended for patients with heart failure and reduced left ventricular ejection fraction to reduce the risk of heart failure hospitalization and death in ambulatory patients who remain symptomatic despite optimal medical treatment.
- However, there is a gap in patients in real life. The clinical characteristics of patients enrolled in clinical trials commonly differ from the ones found in daily clinical practice.

Does it contribute anything new?

- We evaluated the clinical profile of patients treated with sacubitril/valsartan according to hospital type. We also studied the potential role of these differences and of the hospital characteristics in drug safety and effectivity.
- The use of sacubitril/valsartan in real life showed a low rate of events during follow-up. The above suggests that this drug is safe and beneficial in different clinical profiles of patients but drug withdrawal is more frequent in medium/small size hospitals.
- This supports the use of sacubitril/valsartan in our clinical practice, regardless of our hospital environment.

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Authors' contributions

All authors have made substantial contributions to all of thefollowing:

1) The conception and design of the study, or acquisition ofdata, or analysis and interpretation of data.

2) Drafting the article or revising it critically for importantintellectual content.

3) Final approval of the version to be submitted.

Conflicts of interest

No conflicts of interest associated with this publication. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137–1146.
2. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.
3. Bleumink GS, Knetsch AM, Sturkenboom MCJM, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. The Rotterdam Study. *Eur Heart J*. 2004;25:1614–1619.
4. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics – 2012 update: a report from the American Heart Association. *Circulation*. 2012;125:e2–e220.
5. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63:1123–1133.
6. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2013;15:808–817.
7. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.
8. Sacks CA, Jarcho JA, Curfman GD. Paradigm shifts in heart-failure therapy – a timeline. *N Engl J Med*. 2014;371:989–991.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2016;134:e282–e293.
10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart*. 2016;37:2129–2200.
11. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21:1169–1186.
12. Mahajan R. Real world data: additional source for making clinical decisions. *Int J Appl Basic Med Res*. 2015;5:82.
13. Vicent L, Esteban-Fernández A, Gómez-Bueno M, et al. Clinical profile of a nonselected population treated with sacubitril/valsartan is different from PARADIGM-HF trial. *J Cardiovasc Pharmacol*. 2018;72:112–116.
14. Yandrapalli S, Aronow WS, Mondal P, et al. Limitations of sacubitril/valsartan in the management of heart failure. *Am J Ther*. 2017;24:e234–e239.
15. Filippatos G, Farmakis D, Parissis J, et al. Drug therapy for patients with systolic heart failure after the PARADIGM-HF trial: in need of a new paradigm of LCZ696 implementation in clinical practice. *BMC Med*. 2015;13:35.
16. Iyngkaran P, Liew D, McDonald P, et al. Phase 4 studies in heart failure – what is done and what is needed? *Curr Cardiol Rev*. 2016;12:216–230.
17. Vicent L, Esteban-Fernández A, Gómez-Bueno M, et al. Sacubitril/valsartan in daily clinical practice: data from a prospective registry. *J Cardiovasc Pharmacol*. 2019 Feb;73:118–124.
18. Kristensen SL, Martinez F, Jhund PS, et al. Geographic variations in the PARADIGM-HF heart failure trial. *Eur Heart J*. 2016;37:3167–3174.
19. Díez-Villanueva P, Vicent L, de la Cuerda F, et al. Left ventricular ejection fraction recovery in patients with heart failure and reduced ejection fraction treated with sacubitril/valsartan. *Cardiology*. 2020;145:275–282.
20. Esteban-Fernández A, Díez-Villanueva P, Vicent L, et al. Sacubitril/Valsartan is useful and safe in elderly people with heart failure and reduced ejection fraction: data from a real-word cohort. *Rev Esp Geriatr Gerontol*. 2020;55:65–69.
21. López-Azor JC, Vicent L, Valero-Masa MJ, et al. Safety of sacubitril/valsartan initiated during hospitalization: data from a non-selected cohort. *ESC Heart Fail*. 2019;6:1161–1166.