

Sacubitril/Valsartan for Heart Failure in Patients with Becker Muscular Dystrophy and Dilated Cardiomyopathy: A Case Series

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Abstract

Background: Dilated cardiomyopathy with heart failure is a common cause of morbidity and mortality in patients with Becker muscular dystrophy. An early diagnosis, treatment and a close follow-up are crucial in improving quality of life and prognosis. Neuro-hormonal therapy may improve symptoms and cardiac dysfunction and reduce mortality risk. Little is known about the use of sacubitril/valsartan for heart failure in patients with Becker muscular dystrophy and dilated cardiomyopathy.

Methods: We present a case series of four patients with Becker muscular dystrophy cardiomyopathy followed in a dedicated cardiologic neuromuscular program and treated with sacubitril/valsartan because of severe left ventricular dysfunction with heart failure symptoms.

Results: In our experience sacubitril/valsartan was effective in improving symptoms and functional capacity, in reducing hospital admission for HF and, when early introduced, it promoted positive reverse heart remodeling. Despite a fragile population, sacubitril/valsartan was safe, without episodes of hypotension or renal function worsening.

Conclusion: Sacubitril/valsartan may be considered an effective and safe pharmacological option in patients with Becker muscular dystrophy and dilated cardiomyopathy with reduced ejection fraction.

Keywords: Becker muscular dystrophy • Dilated cardiomyopathy • Heart failure • Sacubitril/valsartan • Cardiac reverse remodeling

Abbreviation: ACE-I: Angiotensin Converting Enzyme Inhibitors; AP: Arterial Pressure; BB: Beta Blockers; BMD: Becker Muscular Dystrophy; BNP: Brain Natriuretic Peptide; CMR: Cardiac Magnetic Resonance; DMD: Duchenne Muscular Dystrophy; ECG: Electrocardiogram; eDV: end-Diastolic Volume; FSS: Fatigue Severity Scale; GLS: Global Longitudinal Strain; HF: Heart Failure; ICD: Implantable Cardioverter Defibrillator; LFE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEF: Left Ventricular Ejection Fraction; MMT: Manual Muscle Testing; MRC: Medical Research Council; NYHA: New York Heart Association; RV: Right Ventricle; S/V: Sacubitril/Valsartan; 6MWT: 6-Minutes Walking Test

Introduction

Becker Muscular Dystrophy (BMD) is an inherited disorder, caused by dystrophin deficiency due to in-frame deletions, mutations or duplications in the DMD gene (Xp21.2), leading to a quantitative and/or qualitative protein dysfunction with consequent muscle degeneration. BMD shows a wide heterogeneity in its severity. Symptoms may range from limb weakness leading to a loss of deambulation in the late second decade, to myalgia in childhood and young adulthood, with little effect on deambulation until adulthood [1,2]. A coordinated, multidisciplinary approach is essential for the management of BMD [3], the cardiac muscle could also be affected, with the development of cardiomyopathy and/or arrhythmic manifestations. Today, cardiac disease represents the major cause of morbidity and mortality [4,5]. Because of the

peripheral muscle impairment and lung involvement, the suspicion and diagnosis of cardiomyopathy with Heart Failure (HF) is often challenging due to overlapping symptoms and a long-lasting subclinical phase of ventricular dysfunction; in addition, in dystrophic patients, therapeutic course-modifying interventions according to HF guidelines [6] are often problematic because of the complexity of the muscular involvement and a limited knowledge about the approved HF therapy in this specific patients population. Sacubitril/Valsartan (S/V), which showed a reduction in mortality and hospitalization compared with standard therapy [7], is the newest approved drug for HF with reduced Left Ventricular Ejection Fraction (LVEF) [6]. The benefits of S/V have been confirmed in real-world settings [8]. However, only few reports are available in patients affected by dystrophinopathic cardiomyopathy, although most of them described encouraging outcomes [9-11]. We report our experience with the use of S/V in four BMD patients followed in a dedicated cardiologic neuromuscular program

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Received 14 April 2021; **Accepted** 06 May 2021; **Published** 12 May 2021

Case Series

During a four-year period, through a retrospective analysis and chart review of patients referred to a dedicated cardiologic program within Neuromuscular Disease Multidisciplinary Center, we identified four adult patients with BMD who had been diagnosed with dilated cardiomyopathy, complicated by severe left ventricular dysfunction and HF symptoms and, who were treated with S/V. According to the dedicated program, at baseline evaluation, all patients

underwent to clinical assessment, Electrocardiogram (ECG), echocardiogram, blood tests, 6-minutes walking test (6MWT), when practicable, manual muscle testing (MMT) according to Medical Research Council (MRC) and Fatigue Severity Scale (FSS) assessment [12-14]. These evaluations were repeated at each follow-up and, when indicated, Cardiac Magnetic Resonance (CMR) or cardiopulmonary exercise test were performed. Characteristics of patients are reported in Table 1. The study was conducted according to Good Clinical Practice requirements and in compliance with Helsinki Declaration. All patients provided written informed consent to publish the case.

Patient 1

A 26-year-old male patient with BMD was referred to our center in 2018 due to a III NYHA class and left ventricular systolic dysfunction. He reported fatigue and lower extremity muscular weakness. Upon clinical evaluation, he presented mild signs of pulmonary congestion and mild hepatomegaly; Arterial Pressure (AP) was 110/65 mmHg and heart rate was 88 bpm. He had normal renal function, potassium and Brain Natriuretic Peptide (BNP) values. He performed 309 m at 6MWT and the FSS was 5. Echocardiography showed a dilated Left Ventricle (LV) (end-diastolic volume (eDV) of 80 mL/mq, with 35% of LVEF, mild to moderate Right Ventricle (RV) dysfunction (FAC area 28% and TAPSE 16 mm) and mild mitral regurgitation. His therapy included bisoprolol 2.5 mg, valsartan 60 mg, furosemide 25 mg. considering all data; we decided to stop valsartan and furosemide and to introduce S/V 24/26 bis in die (bid). Four weeks later, the patient reported a significant clinical improvement, with an II NYHA class, a FSS of 4 and 341 meters at 6MWT; echo and lab parameters were almost stable, therefore S/V was increased to 49/51 mg bid. Three months later a CMR showed a mild biventricular improvement: a moderate LV systolic dysfunction (38%) in a diffuse hypokinetic LV, with a

thin intramyocardial Late Gadolinium Enhancement (LGE) at intraventricular septum and a mild RV dysfunction (40%).

A slow-but complete-up-titration of S/V to 97/103 mg bid was completed over 4 months. NYHA class improved to I, volume remodelling was accomplished (eDV of 67 mL/mq) and LVEF stabilized at 40%. Six months later, this clinic improvement was confirmed at 6MWT, with 355 m covered, and at the cardiopulmonary test, with a peak VO_2 of 18.4 mL/min/kg. Bisoprolol therapy was increased to 3.75 mg daily. At the one-year follow-up, all positive clinical features were confirmed (NYHA I, FSS 3 and 369 m at 6MWT) and a CMR showed a further improvement, with mild to moderate LV dysfunction (LVEF 43%) and normalization of the RV function (RVEF 55%). The patient completed a two-year follow-up, showing clinical and echocardiographic stability. The introduction of S/V was safe and associated with a progressive clinical improvement that it is crucial, considering the case of a young patient already limited in his daily life by muscular weakness. Moreover, thanks to therapy optimization in an early phase of dilated CMP, we witnessed an inverse LV and RV remodelling and a biventricular function improvement. The increase in systolic function allowed delaying the indication for a primary prevention implantation of an Implantable Cardioverter Defibrillator (ICD).

Patient 2

In 2015, a 21-years-old male patient with BMD was found to have a moderate left ventricular dysfunction. One year later, CMR examination reported a dilated LV with a moderate systolic dysfunction (LVEF 42%) and an extended epicardial-subepicardial LGE at the infero-lateral wall and apex. Because of a reported hypotension, therapy with a low dose ramipril (1.25 mg daily) was started. The patient was referred to our neuromuscular dedicated

Table 1. Characteristics of Becker Muscular Dystrophy patients with dilated cardiomyopathy and severe left ventricular dysfunction treated with sacubitril/valsartan.

Patients		Patient 1	Patient 2	Patient 3	Patient 4
Age at onset of symptoms/signs of BMD (yo)		13	5	13	15
Symptoms or signs at onset of BMD		High CPK level	High transaminase level	Exercise related cramps	Difficult stairs climbing
Age of genetic diagnosis of BMD (yo)		13	5	18	23
Mutations of DMD gene		Deletion of exons 45-53	Deletion of exons 3-7	Deletion of exons 47-49	Deletion of exons 45-53
Age at first diagnosis of cardiac involvement (yo)		17	11	61	56
Comorbidity		None	None	None	None
Age at S/V introduction (yo)		26	26	63	59
S/V (dose and uptitration)		24/26 mg bid, uptitrated to 97/103 mg bid at 4 months	24/26 mg bid	49/51 mg bid	49/51 mg bid uptitrated to 97/103 mg bid at 6 months
Last follow-up (months)		24	6	24	18
NYHA class	at T_0	III	I	III	III
	at last follow-up	I	I	II	II
Blood pressure (mmHg)	at T_0	110/60	100/65	115/70	140/90
	at last follow-up	105/60	110/70	115/70	110/70
BNP (pg/mL)	at T_0	24	10	226	110
	at last follow-up	23	9	485	74 (NtproBNP)
Creatinine (mg/dl)	at T_0	0,6	0,7	0,5	0,6
	at last follow-up	0,7	0,7	0,8	0,5
LVEF (%)	at T_0	35	35-38	30	32
	at last follow-up	43	42	45	32
LVEfV (ml/mq)	at T_0	80	78	54	93
	at last follow-up	64	72	42	77
Right ventricle dysfunction*	at T_0	Yes	No	Yes	No
	at last follow-up	No	No	No	No
6MWT (m)	at T_0	309	468	NA	NA
	at last follow-up	365	484	NA	NA
FFS	at T_0	5	1.3	4.7	4.6
	at last follow-up	3	1.1	3.3	3.8
MMT upper limbs	at T_0	5	5	4	4
	at last follow-up	5	5	4	4
MMT lower limbs	at T_0	4	5	3	3
	at last follow-up	4	5	3	3

center in 2019, when he presented an I NYHA class, a LVEF of 45%, an heart rate of 65 bpm and normal lab values. Despite baseline values of blood pressure (AP=100/65 mmHg), he was encouraged to increase ramipril to 2.5 mg daily. In 2020, at his routine annual visit: NYHA class was I, his fatigue perception at FSS was 1.3 and, the blood pressure was stable (AP=105/80 mmHg). He had a good performance at 6MWT, with 468 m covered. However, a mildly dilated (eDV 78 mL/mq) and hypokinetic LV with EF of 35-38% and a Global Longitudinal Strain (GLS) of -15% was found. Mitral regurgitation was mild. We stopped ramipril and started S/V 24/26 mg bid.

Thirty days after the introduction of S/V, the patient referred stable clinical condition; moreover, despite a low basal blood pressure, the drug was well tolerated. Three months later, CMR showed an improved LVEF of 44% with unmodified epicardial-subepicardial LGE at the inferolateral wall and apex (Figure 1). The RV appeared mildly dilated, with normal pump function. The dose was not changed, due to AP values of 105/70 mmHg. At 6 months follow-up visit all clinical, functional and laboratoristic parameters were stable. The echocardiographic evaluation confirmed a mild inverse remodelling (LVEV 72 mL/mq) with moderate LV dysfunction (LVEF 42%) and normal RV performance. In this case, S/V was used in order to obtain a substantial positive effect on inverse LV remodelling and pump function, considering the young age of the patient. The LVEF improvement allowed, also in this case, delaying the need of ICD implantation.

Patient 3

In 2016, a 61-years-old man with BMD and severe muscular involvement was implanted for paroxysmal III degree atrioventricular block. At that time, he presented mild left ventricular dysfunction (LVEF 50%). In 2018 he complained dyspnoea on mild exertion (NYHA III) with a FSS of 4.7; at echo, LVEF was 30% with mild RV impairment. The rate of ventricular pacing was 15%. Renal function was normal and BNP value 226 pg/ml. The patient was assuming furosemide 25 mg, spironolactone 50 mg, olmesartan 20 mg and amlodipine 5 mg. The antihypertensive drugs were stopped and S/V 49/51 mg bid was introduced. Three months later, LVEF was 45%, NYHA changed from III to II and FSS was 3.3. These values remained stable since his last evaluation, at 2-years follow up. This case report shows the safe use of S/V in an older patient with severe functional limitation due to muscular dystrophy. It also confirms the significant clinical and echocardiographic improvement related to S/V, when introduced early, as soon as the dysfunction is identified.

Patient 4

In 2016, a 56-years-old patient with BMD was diagnosed with a dilated cardiomyopathy complicated by severe LV systolic dysfunction; in the same year he underwent to ICD implantation for primary prevention. The patient had a severe functional limitation due to dyspnoea and muscular impairment. In 2017 and 2018 he was also hospitalized for episodes of worsening HF, requiring IV diuretics. In 2019 the patient came to our attention. He was a III NYHA class, with a FSS of 4.6. Blood pressure was 140/90 mmHg and his therapy

included bisoprolol 3.75 mg, ramipril 5 mg, furosemide 25 mg, spironolactone 25 mg. Upon the echocardiographic evaluation, he presented a dilated (eDV 93 mL/mq) and severely impaired (EF 32%) LV with a normocinetic RV. Mild to moderate mitral regurgitation was also present. Renal function was normal. He had moderate-severe legs muscle weakness, hyperlordosis, waddling gait. We introduced S/V 49/51 mg bid and we suspended furosemide. The patient soon reported a clinical improvement, with an II NYHA class and a FSS of 3.8, regular blood pressure values and normal lab parameters at a 6-month evaluation. S/V was up-titrated to maximal dosage. One year later, clinical conditions were stable with II NYHA class and no hospital admissions for HF. Left ventricular systolic function was unchanged, while mitral regurgitation was mild. The patient reported a further clinical improvement in functional capacity. These data were all confirmed at the 18-month follow-up evaluation. In this case, S/V was used at later stage of BMD cardiomyopathy when the objective was to improve the clinical status and reduce hospital admissions for heart failure worsening, with an evident gain in quality of life.

Discussion

Becker Muscular Dystrophy is related to dystrophin mutations resulting in an abnormal and less functional protein. Compared to Duchenne Muscular Dystrophy (DMD) patients in whom dystrophin is totally absent and muscular involvement is severe and has an early onset, BMD patient's typically present late- and often not limiting- muscular weakness [1]. Cardiomyopathy in BMD is more frequent and severe compared to Duchenne and may precede skeletal muscle decline. Cardiomyopathy with refractory HF is the leading cause of death in BMD. Becker patients with cardiomyopathy usually received the accepted standard HF therapy. Systematic review and metanalysis have shown that Angiotensin Converting Enzyme Inhibitors (ACE-I), angiotensin receptor blockers, Beta-Blockers (BB) and/or aldosterone antagonists tend to improve or preserve left ventricular systolic function and delay the progression of dystrophinopathic cardiomyopathy [15,16]. In symptomatic Class IV HF, symptoms and LVEF improve transiently when ACE-I and BB therapy are initiated. However, the certainty of the evidence is very low due to the paucity of trials, the small numbers of participants studied and the lack of hard endpoint as survival. Therefore, cardiac management remains highly variable and, generally, underused [2-5].

Over the last years, S/V has been found to improve both survival and quality of life and to reduce hospitalisation when compared to an ACE-inhibitor in patients with chronic HF and reduced LVEF [7], which resulted in its introduction in HF treatment guidelines [6]. Little is known about the use of S/V for HF in dystrophic patients. The main findings of S/V use in our four BMD cases analysis series are related to the following main aspects. First, our experience shows the safety of S/V in this fragile population; no clinical significant hypotension, nor any renal failure were described. Probably, the absence of adverse events was also favoured by a slow up-titration of the drug, when feasible, which allowed patients to progressively get used to the

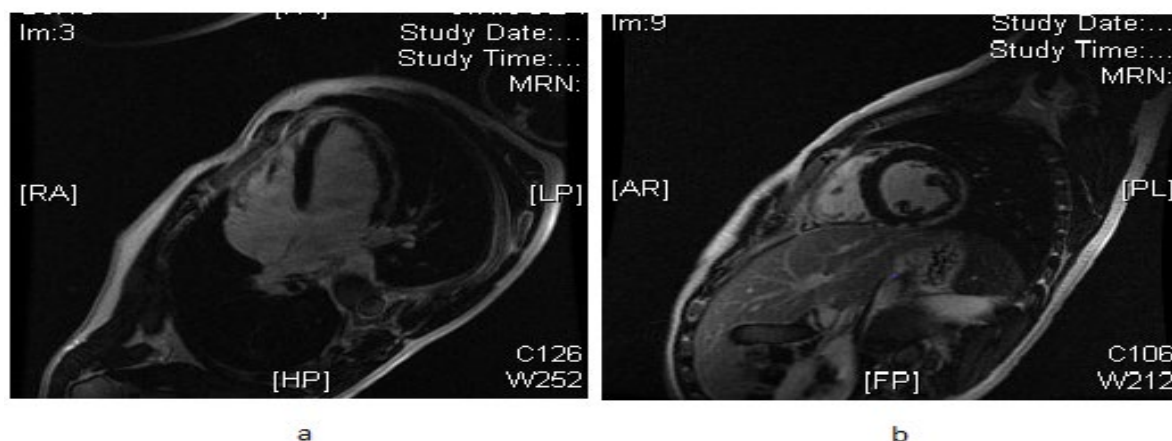


Figure 1. Images of cardiac magnetic resonance belonging to patient 2 and showing late gadolinium enhancement at inferolateral wall and apex in a four-chamber (a) and in a short-axis view (b).

hemodynamic effects of S/V. Secondly, we noted the effects of S/V in cardiac reverse remodeling and in gain in pump function when the drug is used in an early phase of dilated cardiomyopathy, especially in young BMD patients, as it was previously demonstrated in the general HF population [17-19]. Sacubitril/valsartan has been shown to reduce profibrotic signalling in HF with reduced ejection fraction, which may contribute to the improved outcomes in treated patients [20]. Becker cardiomyopathy pathology includes the development of subepicardial fibrosis in the inferolateral wall first, and, then, its progressive diffusion.

Myocardial fibrosis correlates with LVEF decline: an early recognition of cardiac involvement and treatment with S/V of BMD patients may slow this process and the progress towards refractory HF. The use of S/V in a larger cohort of BMD patients would be desirable to confirm these potential effects. Moreover, the early introduction of S/V, by promoting a significant improvement in ventricular function, may delay the indication of ICD implantation for primary prevention. Lastly, S/V use was associated with a significant improvement in term of functional capacity, and dyspnoea. This population is already fatigued, due to a long history of limbs and respiratory muscular weakness. Thus, in these patients it is worthy of remark the effect of S/V in reducing HF symptoms that usually aggravate the neuromuscular involvement, further limiting daily activities and quality of life. In our population of BMD patients, BNP was a less sensitive biomarker in detecting severe cardiomyopathy, as previously reported [21,22]. Low values were detected at baselines evaluation, despite severe left ventricular dysfunction, and, moreover, along the follow-up the variation of BNP after S/V introduction was not significant. Further studies are needed to explain the precise mechanism of this finding.

We compared our data with literature findings. We only found a study by Papa et al., who treated a single BMD patient with S/V [10]. The patient presented very rapid clinical and echocardiographic improvements only 30 days later. In our experience clinical and echocardiographic improvements were already evident in the first months of drug administration, also at low doses, and benefits progressively increased over time, and with the titration of the therapy. No further data are available on the use of S/V in BMD patients. However, considering the common etiology of Becker and Duchenne dystrophy and the similar cardiac involvement, our data are aligned with the experience of Lamendola et al., who administered S/V to three young asymptomatic Duchenne patients, with significant improvement of LV function and remodeling [9]. Moreover, we present data resulting from a longer follow-up than the ones reported by other authors [9,10]. In our case series, the use of S/V is safe: all patients did not present symptomatic or asymptomatic hypotension or arrhythmic complications, as previously reported in a Duchenne patient [11].

Conclusion

Our experience suggests that S/V may be considered an effective and safe pharmacological option in patients with BMD and dilated cardiomyopathy with reduced ejection fraction, since it could promote symptoms control and functional improvement, as well as -when early introduced- an increase in LV and RV function and positive reverse heart remodeling.

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How to cite this article: Maria Vittoria Matassini, Michela Coccia, Michela Aringolo, and Matilda Shkoza, et al. "Sacubitril/Valsartan for Heart Failure in Patients with Becker Muscular Dystrophy and Dilated Cardiomyopathy: A Case Series." *Clin Case Rep* 11 (2021): 1439.