CASE REPORT

Beneficial effects of one-month sacubitril/valsartan treatment in a patient affected by end-stage dystrophinopathic cardiomyopathy

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Dystrophinopathic cardiomyopathy (DCM) is an almost constant manifestation in Becker muscular dystrophy (BMD) patients significantly contributing to morbidity and mortality. The nearly complete replacement of the myocardium by fibrous and fatty connective tissue results in an irreversible cardiac failure, characterized by progressive reduction of the ejection fraction. According to PARADIGM-HF trial results, the European Society of Cardiology (ESC) guidelines recommend the use of sacubitril/valsartan in ambulatory patients with heart failure and reduced ejection fraction, who remain symptomatic despite an optimal medical therapy. To date, little is still known about the use of sacubitril/valsartan in DCM. We report the case of a patient with dystrophinopathic end stage dilated cardiomyopathy with reduced ejection fraction who successfully responded to sacubitril/valsartan treatment.

Key words: dystrophinopathic cardiomyopathy, heart failure, sacubitril/valsartan, Becker muscular dystrophy

Conflict of interest
The Authors declare no conflict of interest

How to cite this article: Papa AA, Gallinoro E, Palladino A, Golino P. Beneficial effects of one-month sacubitril/valsartan treatment in a patient affected by end-stage dystrophinopathic cardiomyopathy. Acta Myol 2020;39:136-40. https://doi.org/10.36185-2532-1900-018

Introduction

Dystrophynopathies are X-linked recessive disorders characterized by partial (benign dystrophinopathy, BMD) or total (severe dystrophinopathy, DMD) dystrophin deficiency [1]. Cardiac involvement is a common finding in muscular dystrophies [2] and often precedes the skeletal muscle one; in dystrophinopathies, left ventricular systolic dysfunction leading to dilated cardiomyopathy (DCM) and intractable heart failure represents the typical picture [2-4]. Patients may often require the use of mechanical devices [5-6] or need heart transplantation [7]. In late stages, DCM may be complicated by atrial fibrillation or atrial flutter, and/or by ventricular arrhythmias, that predispose the patients to an increased risk of sudden cardiac death [8].

Despite mild muscle symptoms, over 70% of patients with BMD develop dystrophinopathic cardiomyopathy, that evolves toward the picture of an intractable heart failure [3], regardless an appropriate pharmacological treatment [9]. Given the lack of specific guidelines on the issue, the treatment of dystrophinopathic DCM usually follows the general guidelines for treating genetic cardiomyopathies [10].

Sacubitril/valsartan (LCZ696) (SAV) has recently been approved for the treatment of patients with refractory heart failure and reduced ejection fraction (HFrEF), as it showed a reduction in mortality and hospitalization compared with standard drugs [11]. Sacubitril/valsartan belongs to the class of angiotensin receptor-neprilysin inhibitors (ARNi), endopeptidases which cleave natriuretic peptides [11]. The effectiveness and safety of this drug receives constant confirmation in daily practice. However, no data are still available about its possible clinical use in patients affected by dystrophinopathic dilated cardiomyopathy with HFrEF.

We report for the first time the case of a patient with dystrophinopathic dilated cardiomyopathy and HFrEF who successfully responded to sacubitril/valsartan treatment, after just 30 days of therapy.

Case report

A 46-year-young man, affected by familial dystrophinopathic cardiomyopathy, was hospitalised for the exacerbation of signs and symptoms of congestive HF. The patient was followed by the age of 23 years for cardiac symptoms characterized by exertional dyspnoea, and several episodes of tachycardia. The diagnosis of dystrophinopathic cardiomyopathy was made because of family history (the older brother died at the age of 28 from intractable heart failure, awaiting heart transplantation) and confirmed by genetic analysis, that showed the deletion of exons 45-49 of the dystrophin gene, typical of BMD phenotype. The patient had no muscle symptoms. The cardiological investigation showed a dilation of the heart chambers and a reduced ejection fraction, consistent with a picture of dystrophinopathic dilated cardiomyopathy, that was confirmed at the endomyocardial biopsy. Treatment with ACE-inhibitors (delapril 45 mg/die), steroids (deflazacort) and antioxidants (vitamin C and E, and Coenzyme Q10) was promptly set up, obtaining a stabilization of the cardiological parameters for about 12 years.

At the age of 40, a bicameral cardioverter defibrillator (ICD) was implanted because the evidence of severely dilated left ventricular cavity with diffuse hypokinesis and onset of symptoms and signs of HFrEF. In that occasion, the pharmacological therapy of HF was titrated according to ESC guidelines: delapride 30 mg/die, carvedilol 25 mg/die, furosemide 25 mg/die and spironolactone 25 mg/die, obtaining relative well-being for about 5 years.

At the age of 45 years, a cardiorespiratory episode of infectious origin, which required hospitalization in health care facility, further compromised the precarious cardiovascular balance of the patient, who experienced after few months dyspnoea on mild exertion and poor tolerability of daily activities (NYHA class III; basal spo2: 96%; heart
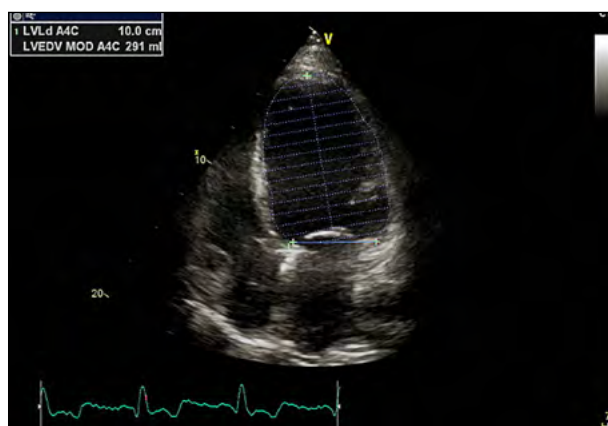
Figure 1. B-mode echocardiography. Enlarged left ventricle with an end-diastolic volume evaluated through the biplane method in apical 4-chambers view (291 ml).

rate (hr): 95 bpm; arterial blood pressure: 110/70 mmhg). Two-dimensional and M-mode echocardiograms showed reduced systolic indices, including fractional shortening (9%) and ejection fraction (EF) (18%) (Fig. 1). Echocardiography showed high filling pressure (E/E' average 27.3) and a global longitudinal strain (GLS) of -6.4% (Fig. 2). Right ventricle function, tricuspid annular plane systolic excursion (TAPSE = 13 mm) and right ventricle velocity (RVs'= 8 cm/s) were also reduced.

ProBNP was 1578 pg/ml. The patient complained a concomitant involvement of motor abilities, with a reduction of the 6MWT (270 meters), SpO2 (92%), and an increase in HR (110 bpm). Exertion was perceived as hard, rated 4-5 on the Borg scale. According to the current indications in patients with HFrEF [28], the therapy with ACE-inhibitors was switched to SAV, 24/26 mg b.i.d.

After 30 days of SAV therapy, the patient referred a dramatic improvement in his symptoms and functional status, with disappearance of dyspnoea for mild effort. The NYHA class changed from III to II. The motor abilities also improved (6MWT up to 315 meters, and SpO2 up to 98%). The exertion was perceived as slight, according to the Borg scale (rate 2). The ProBNP values decreased significantly to 610 pg/ml (Tab. I). The echocardiography showed an improvement in cardiac function: EF increased to 28% with a concomitant increase in stroke volume; GLS confirmed an improvement in left ventricle function showing an Average of -7.5% (Fig. 2). Left ventricle volume and filling pressure were slightly decreased (E/e' 19.8). An improvement in right ventricle systolic function was also recorded (TAPSE 19 mm; RVs'= 11 cm/s) (Tab. I). The drug was well tolerated; none of the common PARADIGM HF side effects was reported. SAV therapy was confirmed and a new evaluation scheduled, at three-month of treatment.

Table I. Clinical and laboratory data at baseline and after 30 days of therapy with sacubitril/valsartan.

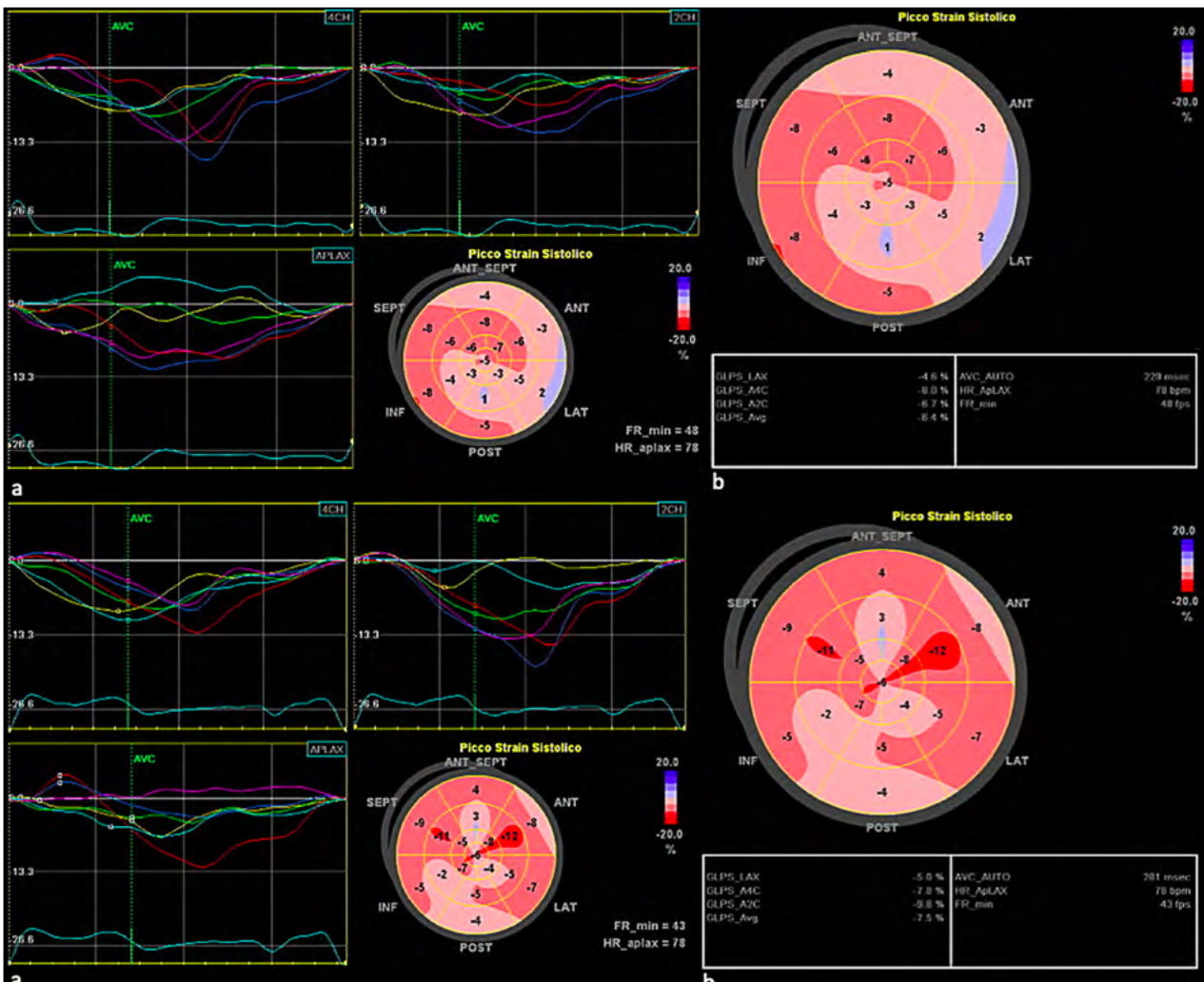|	Baseline	30 days
6MWT		
Heart rate (bpm)		
Baseline	80	75
3 minutes	102	90
6 minutes	110	102
SpO2 (%)		
Baseline	98	98
3 minutes	95	98
6 minutes	92	98
Meters		
3 minutes	136	153
6 minutes	270	315
Dyspnoea	Moderate	Mild
Borg scale	4-5	2
Echocardiographic parameters		
EF (%) **Teicholz** **Biplane**	14 18	23 38
LVEDd (mm)	78	74
LVESd (mm)	73	66
IVSd (mm)	8	8
LVPWd (mm)	10	10
LVEDv (ml)	291	230
LVESv (ml)	236	166
LAVI (ml/m²)	76	68
E/e'	27.31	19.88
TAPSE (mm)	13	19
S' (cm/sec)	8	11
GLS Avg (%)	-6.4	-7.5
Laboratory data		
Serum creatinine (mg/dl)	0.76	0.75
Potassium (mg/dl)	4.5	4.9
BUN (mg/dl)	50	57
Pro-BNP (pg/ml)	1578	610

LVEDd: left ventricular end-diastolic diameter; LVESd: left ventricular end-systolic diameter; IVSd: interventricular septum diameter; LVPWd: left ventricular posterior wall diameter; LVEDv: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LAVI: left atrial volume index; TAPSE: Tricuspid annular plane systolic excursion; GLS Avg: global longitudinal strain average; BUN: Blood Urea Nitrogen

Discussion

The treatment of HF related to myocardial involvement in muscular dystrophies is still challenging and no guidelines exist about this issue. As reported in several papers [11-15], SAV improves the effort tolerance, by reducing both end-diastolic and systolic left ventricle volumes, induces reverse remodelling of SAV on left ventricle [12], in turn resulting into a better quality of life. Furthermore, in patients with chronic HFrEF not related to muscular dystrophies, SAV has shown to be superior to enalapril in reducing mortality and HF hospitalizations [13].

However, little is still known about the safety and effectiveness of SAV in patients with dystrophinopathic cardiomyopathy, in which the reduced mobility due to muscular impairment can be aggravated by the heart failure, further limiting their daily activities.

In the case here reported, the use of SAV produced an improvement in symptoms, NYHA class and motor function. The effectiveness of SAV was also demonstrated by the reduction in pro-BNP plasma levels, associated to a reduction in haemodynamic stress and cardiovascular events [14]. Furthermore, an improvement in longitudinal contraction of cardiomyocytes, an event that may contrib-

Figure 2. Top. GLS at baseline. Longitudinal strain curves (a) and the 17-segments "Bull's eye" (b). A GLS average of -6.4% with systolic dysfunction involving especially the anterior and lateral walls is shown.; Bottom. GLS after 30 days of SAV. An increase in GLS average (-7.5%) with an improvement of anterior and lateral walls longitudinal strain is shown.

ute to the ejection fraction increasing, was seen by GLS. Interestingly, the improvement was mainly observed in the left ventricle at the antero-lateral wall level, while the earlier and most frequent myocardial involvement is usually observed in the infero-lateral wall in dystrophinopathic patients. This result is not unexpected if we consider that a) the anterolateral wall is later involved in the fibrotic process compared to the inferolateral wall, and so it is still able to better respond to SAV therapy; and b) SAV is able to improve myocardial cell vitality and reduce fibrotic degeneration, as reported in some animal models [15].

To our knowledge, this is the first report on the use of SAV in a patient with dystrophinopathic end stage cardiomyopathy and HFrEF. After only 30 days of therapy, the patient experienced an improvement of clinical symptoms, effort tolerance and cardiac performance, confirmed by a comprehensive echocardiographic assessment that included the strain evaluation. No relevant side effects were reported.

The use of SAV in a larger cohort of patients with dystrophinopathic cardiomyopathy is desirable to confirm its efficacy and safety; moreover, it could be a good pharmacological option for patients with refractory HFrEF not suitable for heart transplantation.

Aknowledgments

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