European Review for Medical and Pharmacological Sciences 2020; 24: 9112-9115

Duchenne muscular dystrophy: preliminary experience with sacubitril-valsartan in patients with asymptomatic left ventricular dysfunction

P. LAMENDOLA[1], G.A. LANZA[1,3], V. MELITA[1], A. VILLANO[1], C. PALERMO[2], D. LEONE[2], A. LOMBARDO[1,3], F. PENNESTRÌ[1], F. CREA[1,3], E.M. MERCURI[2,3], M. PANE[2,3]

[1]Department of Cardiovascular Medicine and [2]Department of Pediatrics; Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[3]Università Cattolica del Sacro Cuore, Rome, Italy

Abstract. – OBJECTIVE: Duchenne muscular dystrophy (DMD) is an inherited X-linked recessive neuromuscular disease caused by mutations of the dystrophin gene, leading to early and progressive muscle deterioration and dilated cardiomyopathy. The aim of this investigation was to assess whether treatment with sacubitril/valsartan (S/V) is well tolerated and may have beneficial effects in DMD patients with left ventricle (LV) dysfunction.

PATIENTS AND METHODS: We administered S/V to 3 DMD patients (19-29 yeard old) with LV ejection fraction <35% at echocardiography but no symptoms of heart failure. All patients were on optimal medical therapy. S/V was initiated at a very low dose of 12/13 mg/die, after withdrawal of angiotensin-converting enzyme inhibitor therapy, and slowly titrated to the dose of 49/51 mg twice daily or the maximally tolerated dose. Clinical and echocardiographic follow-up was performed after 3, 6 and 12 months.

RESULTS: At baseline, the LV ejection fraction was 32±1%. A significant improvement of LV ejection fraction was observed at 3 months (44.0±6.0%; $p<0.05$), which was maintained at 6 (45.7±5.0%) and 12 (43.3±3.2%) months ($p<0.05$ for both). No relevant side effects were reported throughout the period of the study.

CONCLUSIONS: Our preliminary data suggest that, in DMD patients with reduced LV ejection fraction, S/V is safe and may improve LV function.

Key Words:
Left ventricular dysfunction, Duchenne muscular, Dystrophy, Sacubitril/valsartan.

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder, related to mutations in the dystrophin gene, characterized by progressive weakness, with loss of ambulation and progressive respiratory impairment. Cardiac involvement is characterized by dilated cardiomyopathy, which has become the most frequent cause of death[1]. The use of angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers and eplerenone has been reported to reduce LV dysfunction in patients with preclinical cardiomyopathy[2-4]. Sacubitril/valsartan (S/V) is an angiotensin-receptor/neprilysin inhibitor that has been found to improve survival, as compared to an ACE-inhibitor in patients with chronic heart failure and reduced LV ejection fraction[5,6].

In this preliminary study, we assessed whether S/V therapy can be prescribed safely and may have favorable effects on LV function in asymptomatic patients with LV dysfunction.

Patients and Methods

We administered S/V in 3 DMD patients who showed a significant impairment of LV function (LV ejection fraction lower than 35% at transthoracic echocardiography) in the absence of any apparent symptoms and signs of heart failure. The patients did not have any parental relationship and the diagnosis of DMD had been confirmed in all by showing typical dystrophin mutations by multiplex ligation-dependent probe amplification genetic testing on a blood sample[7]. All patients were on optimal medical therapy, as suggested by the DMD care recommendations[8], including a beta-blocker, an ACE-inhibitor and a mineralocorticoid receptor antagonist, together with furosemide, for more than 12 months, with

Corresponding Author: Gaetano A. Lanza, MD; e-mail: gaetanoantonio.lanza@unicatt.it

no appreciable changes in LV systolic function. All patients had night time respiratory support with bilevel continuous positive airway pressure ventilation. Blood samples showed no significant impairment of both liver and kidney function and electrolyte levels were also in the normal range. An assessment of systolic blood pressure values in the previous month showed constant values ≥ 100 mmHg, which was confirmed during the hospitalization.

S/V was initiated, with very slow titration while patients were admitted at the Neuromuscular Pediatric Unit of our University Hospital.

The ACE-inhibitor was withdrawn and S/V was initiated after 36 hours of wash-out, with a starting dose of 12/13 mg once daily. The drug was progressively titrated to the dose of 49/51 mg twice daily or to the maximally tolerated dose by increasing the dose by 12/13 mg/die twice daily every 2 weeks. Patients were monitored every 10 days until reaching the maximum tolerated dose, then every month, with no significant alteration of potassium and cystatin serum levels.

Clinical assessment and transthoracic echocardiographic color-Doppler examination, with the aid of Sonovue in 2 patients due to a suboptimal echocardiographic window, were performed before starting the treatment and 3, 6 and 12-month follow-up. The study was approved by the local Ethical Committee.

Results

The individual data of patients are summarized in Table I. Patients were 19, 23 and 29 years old, respectively. At baseline, LV ejection fraction ewas 32±1% (Simpson method). One patient showed moderate LV chamber dilatation, while the other 2 patients showed normal LV volumes.

During 1-year treatment, there was no need to reduce or withdraw the drug because of hypotension or other side effects. Respiratory function was stable.

A complete echocardiography study was repeated at 3, 6 and 12 months. LV ejection fraction was compared by analysis of variance (ANOVA) with a repeated-measure design and multiple comparisons were done by paired *t*-test. A p-value <0.05 was considered as statistically significant.

There was a significant improvement of LV ejection fraction throughout the period of obser-

Table I. Main basal echocardiographic data and changes in left ventricular volumes and ejection fraction during follow-up.

	Patient 1	Patient 2	Patient 3	Average
Basal ECHO data				
LV EDD (mm)	61	58	53	57.3
LV ESD (mm)	50	47	45	47.3
LV PW (mm)	8	9	8	8.3
IVS (mm)	9	9	7	8.3
LAV (ml)	55	41	29	
TAPSE (mm)	25	21	23	23
LV EDV (ml)	153	119	94	122
LV ESV (ml)	101	80	63	81.3
LVEF (%)	34	34	33	33.7
3-month ECHO data				
LVEDV (ml)	136	86	114	112
LVESV (ml)	71	45	72	62.7
LVEF (%)	48	47	37	44
6-month ECHO data				
LVEDV (ml)	132	81	110	107.7
LVESV (ml)	66	43	67	58.7
LVEF (%)	50	47	40	45.7
12-month ECHO data				
LVEDV (ml)	131	99	111	113.7
LVESV (ml)	69	59	65	64.3
LVEF (%)	47	41	42	43.3

LV=left ventricle; EDD=end diastolic diameter; ESD=end systolic diameter; PW=posterior wall; IVS=interventricular septum; LAV=left atrial volume; TAPSE=tricuspid annular plane systolic excursion; EDV=end diastolic volume; ESV= end systolic volume; EF=ejection fraction.

vation (p=0.01). The improvement was already present after 3 months (44.0±6.0%; p<0.05) and was maintained both at 6-month (45.7±5.0%; p<0.05) and 12-month follow-up (43.3±3.2%; p<0.05), with an average increase, after 12 months, of 9.7±2.9% (p<0.05 for both). A reduction of LV volumes was also observed in the patient with initial LV dilatation. No relevant side effects, in particular hypotension or hyperkalemia, were reported throughout the period of the study.

Conclusions

Our preliminary data suggest that S/V may produce a significant improvement of LV function and remodeling in DMD patients without overt heart failure, in whom conventional therapies fail to reduce or halt the progressive impairment of LV function. The drug appears to be safe when a careful slow titration and strict monitoring of blood pressure, electrolytes and renal function is performed. Further studies in larger cohorts, however, are needed to confirm our preliminary findings.

Clinical course of DMD is characterized by a progressive loss of deambulation, most frequently occurring in the second decade, and impairment of respiratory function, but the use of ventilatory support has significantly improved clinical outcome of these patients. On the other hand, cardiac involvement in DMD patients may lead to progressive cardiomyopathy and/or arrhythmias. Because of the reduced functional capacity caused by skeletal muscle disease, however, symptoms of heart failure are often lacking for a long time, and early detection of impaired LV function is often achieved only by routine diagnostic cardiac imaging methods.

Importantly, there are no validated therapies for severe LV dysfunction and remodeling in DMD patients and limited data are also available in patients with preserved LV function. In a randomized study, however, perindopril was found to have a beneficial impact on mortality in patients with preserved LV function[1]. Furthermore, the addition of eplerenone was also able to prevent LV dysfunction in patients with preclinical cardiomyopathy[2]. At present, however, most DMD patients develop progressive cardiac LV dysfunction despite standard and optimal medical therapy; accordingly, the need for new therapies is mandatory.

Sacubitril/valsartan (S/V) is the first angiotensin-receptor/neprilysin inhibitor, a new therapeutic class of drugs[3], that has been found to improve survival, as compared to angiotensin converting anzyme (ACE) inhibitor therapy, in patients with chronic heart failure and reduced LV ejection fraction[4], also showing an excellent safety profile[5].

Our data show that S/V might be helpful also in DMD patients, even when they have not yet developed symptoms of heart failure. In this initial experience with the drug, indeed, we found a significant improvement of LV function after 3 months of therapy, that persisted at 1-year follow-up, in DMD patients with impaired LV ejection fraction. Importantly, the drug was well-tolerated, although it should be underscored that we were very careful in slowly increasing the dose. Thus, our data suggest that a large study on the hemodynamic and clinical effects of S/V in DMD patients with LV dysfunction would be desirable.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Mavrogeni SI, Markousis-Mavrogenis G, Papavasiliou A, Papadopoulos G, Kolovou G. Cardiac involvement in duchenne muscular dystrophy and related dystrophinopathies. Methods Mol Biol 2018; 1687: 31-42.

2) Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, Berard C, Vaksmann G, Weber S, Bécane HM. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. Am Heart J 2007; 154: 596-602.

3) Raman SV, Hor KN, Mazur W, He X, Kissel JT, Smart S, McCarthy B, Roble SL, Cripe LH. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: results of a two-year open-label extension trial. Orphanet J Rare Dis 2017; 12: 39.

4) Dittrich S, Graf E, Trollmann R, Neudorf U, Schara U, Heilmann A, von der Hagen M, Stiller B, Kirschner J, Pozza RD, Müller-Felber W, Weiss K, von Au K, Khalil M, Motz R, Korenke C, Lange M, Wilichowski E, Pattathu J, Ebinger F, Wiechmann N, Schröder R; German Competence Network for Congenital Heart Defects and the Treat-NMD Neuromuscular Network Investigators list of additional local Investigators and co-workers of the German Competence Network for Congenital Heart Defects and the Treat-NMD Neuromuscular Network. Effect and safety of treatment

with ACE-inhibitor Enalapril and β-blocker metoprolol on the onset of left ventricular dysfunction in Duchenne muscular dystrophy - a randomized, double-blind, placebo-controlled trial. Orphanet J Rare Dis 2019; 14: 105.

5) Böhm M, Young B, Jhund PS, Scott D Solomon, Jianjian Gong, Martin P Lefkowitz, Adel R Rizkala, Jean L Rouleau, Victor C Shi, Karl Swedberg, Michael R Zile, Milton Packer, John JV McMurray. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. Eur Heart J 2017; 38: 1132-1143.

6) McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile ML, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371: 993-1004.

7) Lalic T, Vossen RH, Coffa J, Schouten JP, Guc-Scekic M, Radivojevic D, Djurisic M, Breuning MH, White SJ, den Dunnen JT. Deletion and duplication screening in the DMD gene using MLPA. Eur J Hum Genet 2005; 13: 1231-1234.

8) Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM, DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol 2018; 17: 347-361.