Angiotensin receptor-neprilysin inhibitor in symptomatic patients with Duchenne dilated cardiomyopathy: A primetime

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Abstract

Aims Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder, characterized by significant long-term cardiac involvement. Dilated cardiomyopathy (DCM) is the main cause of death in DMD, and angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers (BB) are first-line treatments in DCM. It is unknown whether angiotensin receptor-neprilysin inhibitor (ARNi) could provide greater benefits in this setting. Our aim is to assess whether ARNi use may prevent deterioration in ejection fraction (EF) or is associated with EF improvement compared with ACEi in DMD patients with heart failure and to report the tolerability of ARNi in this group of patients.

Methods and results We followed 22 DMD patients, 6 of them with an EF < 40% and 16 with an EF > 40%. The first group received ARNi on top of BB, while the control group started or continued first-line therapy with ACEi ± BB. From December 2016 to December 2021, we recorded EF values at baseline and at follow-up, comparing EF changes. Median follow-up was 7 months (interquartile range 4.7–9.1). At baseline, the mean of EF (%) in the ARNi group was 31 ± 2%, while it was 59 ± 9% in the control group. At follow-up, we recorded an EF improvement in the ARNi group (38 ± 6%, P-value < 0.05). Among controls, EF at follow-up was substantially unchanged from baseline.

Conclusions Our data suggest that the use of ARNi in DMD patients with DCM and an EF < 40% might be associated with an EF improvement and a safe tolerability profile.

Keywords Duchenne dilated cardiomyopathy; Angiotensin receptor-neprilysin inhibitor; Ejection fraction

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder that affects 1/5000 newborn males and is the most common and severe type of muscular dystrophy. It is characterized by the absence of the protein dystrophin in the muscle membranes, which results in skeletal and cardiac muscle cells death, thereby replaced by fibro-fatty tissue. Clinically, DMD patients present early-onset proximal muscle weakness and significant long-term pulmonary and cardiac involvement.1 Nowadays, the advancement in the early pharmacological treatment and the use of non-invasive ventilation have prolonged DMD patients’ life expectancy, leading however to advanced heart failure (HF) and dilated cardiomyopathy (DCM) as the main cause of death.2,3 An early detection of cardiomyopathy is often challenging. Although histological evidence of cardiac involvement is present early on the natural history of this disease, echocardiographic abnormalities and cardiovascular symptoms (of difficult identification, considering mobility impairment in these patients) are usually delayed until the second decade of life.4 Moreover, no specific guidelines on therapy of DMD cardiac involvement are available. Thus, medical treatment for HF in DMD is based on non-ischaemic DCM, with angiotensin-converting enzyme inhibitors (ACEi) and beta-blockers (BB) as first-line therapy. However, compared
with ACEi, angiotensin receptor-neprilysin inhibitor (ARNi) has demonstrated a greater reduction in the risk of cardiovascular death and HF hospitalization in patients with symptomatic systolic dysfunction.5

**Aims**

Our aim is to assess whether ARNi use in DMD patients is safe and prevents deterioration in ejection fraction (EF) or is associated with EF improvement.

**Methods**

We followed 22 DMD patients between 9 and 37 years old, 6 of them with an EF < 40% and New York Heart Association (NYHA) class II–III and 16 with an EF > 40% and NYHA class I–II. The first group (EF < 40%, symptomatic) started ARNi (24/26 mg 1/2 pill two times/day), titrated up to the maximum tolerated dose, ±BB, stopping ACEi. The control group (EF > 40%, asymptomatic or mildly symptomatic) started or continued first-line therapy with ACEi ± BB. From December 2016 to December 2021, we recorded EF values at baseline and at a follow-up visit for both the two groups. Baseline characteristics at baseline were compared by t-test or χ² to test continuous and categorical variables, respectively. Mean of EF at baseline and follow-up visit in each group was compared using a t-test. A t-test was also used to compare the EF variation in percentage units \([\text{EF}_{\text{baseline}} - \text{EF}_{\text{follow-up}}]\) between the ARNi group and the control one.

**Results**

Median follow-up was 7 months (interquartile range 4.7–9.1). At baseline, the mean of EF (%) in the ARNi group was 31 ± 2%, while it was 59 ± 9% in the control group (Table 1). Duration of corticosteroids treatment between the two groups was comparable.

At follow-up, we recorded an EF improvement in all patients of the ARNi group (38 ± 6%, P-value < 0.05), without side effects and with a good tolerance of the drug. Between controls, the EF average at follow-up was substantially unchanged from the baseline (69 ± 6%, P-value 0.98) (Figure 1). The difference in the mean of EF variation between the two groups was statistically significant (P-value < 0.05).

**Discussion**

Duchenne cardiomyopathy is nowadays the main cause of death in DMD patients. The only curative therapy for advanced HF with reduced EF, that is, heart transplantation, is generally prohibited for DMD, due to the several practical and ethical implications of the disease. It is thereby important to find the best pharmacological therapy to delay deterioration of clinical conditions in these patients.

European Society of Cardiology (ESC) Guidelines do not differentiate heart involvement in DMD from any other form of non-ischaemic DCM and recommend in these patients ACEi/ARNi, BB, mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2i) to improve survival.6

According to the most recent National Heart, Lung, and Blood Institute (NHLBI)/Parent Project Muscular Dystrophy

**Table 1** Baseline characteristics

| Demographics | ARNi 6 patients | ACEi 16 patients | P-value |
|--------------|----------------|-----------------|---------|
| Age, mean (SD) | 22.8 (4.6) | 14.6 (6.7) | 0.01 |
| Female | 0 (0%) | 1 (6%) | 0.53 |
| Clinical | | | |
| EF, mean (SD) | 31.0 (2.2) | 59.5 (9.5) | <0.001 |
| BMI (kg/m²), mean (SD) | 20.6 (2.3) | 22.7 (7.8) | 0.54 |
| Deambulation | 0 (0%) | 7 (44%) | 0.05 |
| Laboratory values | | | |
| Creatinine (mg/dL), mean (SD) | 0.11 (0.01) | 0.21 (0.10) | 0.027 |
| Cystatin C (mg/L), median (IQR) | 1.05 (0.85–1.44) | 0.78 (0.74–0.97) | 0.17 |
| Haemoglobin (g/dL), median (IQR) | 12.4 (11.7, 13.4) | 13.9 (13.1, 14.1) | 0.046 |
| Treatments | | | |
| Beta-blocker | 6 (100%) | 13 (87%) | 0.35 |
| Aldosterone antagonist | 2 (33%) | 1 (7%) | 0.11 |
| Cortisone | 3 (60%) | 12 (75%) | 0.52 |
| Duration of therapy (years), mean (SD) | 10.2 (6.8) | 8.6 (4.9) | 0.60 |
| Diuretics | 1 (17%) | 1 (7%) | 0.48 |

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; EF, ejection fraction; IQR, interquartile range.
ACEi or angiotensin receptor blockers (ARBs) are a first-line therapy for the treatment of heart disease associated with DMD. In this setting, corticosteroids are also known to improve respiratory and cardiac function.

However, compared with ACEi, ARNi has demonstrated a greater reduction in the risk of death and hospitalizations, in patients with symptomatic HF and reduced EF. It is not known whether this might be applicable to DMD patients with HF, providing additional benefits in this particular setting. In a recent survey on the therapeutic approaches to DMD, ARNi has been considered only by 23% of providers when EF was below 40%, highlighting a great variability in terms of therapeutic approaches and the need for more harmonized practices.

Our aim has been to investigate the efficacy and tolerability of ARNi compared with ACEi in DMD patients.

We started ARNi in DMD patients, already using ACEi, with detectable signs of HF (EF < 40%). These patients have been compared with patients showing an EF > 40%, treated with current first-line therapy with ACEi ± BB, as recommended by guidelines. Of note, early treatment of DMD patients aged from 9.5 to 13 years with an ACEi was reported to delay the onset and progression of left ventricular (LV) dysfunction and showed to reduce 10 year risk of mortality.

There is evidence in support of the beneficial effects provided by ARNi treatment in terms of remodelling, EF, and global longitudinal strain (GLS) improvement in DMD patients. ARNi treatment may also contribute to delay cardiac fibrosis in these patients, as recently hypothesized. However, to the best of our knowledge, our report is one of the first attempting to compare ACEi and ARNi in DMD patients. We recognize the limit of an LV dysfunction estimation only by EF measure, but in most cases, inadequate echocardiographic windows did not allow a reliable evaluation of novel echocardiographic indices, such as GLS.

Comparing the two groups, we aimed to detect the absence of an EF deterioration in DMD patients treated with ARNi, so that an additional therapeutic option might be underscored, particularly when standard therapy with ACEi ± BB loses effectiveness. Indeed, progressive LV dysfunction can be detected in these patients despite treatment with ACEi ± BB.

Our results show in the ARNi group not only a detectable stabilization of heart function but also an improvement of EF value at follow-up. Namely, this signal might be interpreted as a way to provide additional time of clinical well-being, as long as the time of EF improvement. In the long term, DMD is a terminal disease, and, at the end, it is characterized by a framework of advanced HF. ARNi may provide longer time free from EF deterioration and potentially from HF symptoms, when response to other therapies is blunted.

Moreover, no side effects have been recorded. All patients tolerated the drug administration (correctly titrated), without hypotension and electrolytic alterations (such as hyperkalaemia) at follow-up, and without particularly interactions with other drugs. However, a careful blood pressure monitoring should be performed at least twice a day in patients using ARNi since recurrent hypotension has been reported as a potential side effect.

This brief report is limited by the crude assessment of EF difference and the heterogeneity of follow-up time, but most of the baseline characteristics of patients were comparable within our groups. It is also important to highlight that DMD is a rare disease and that HF in this setting has not been extensively studied so far. Our results primarily aim to provide a report of safety as well to prompt testing more recent therapies in a specific and often neglected subgroup of pa-
tients in which HF treatment is highly challenging, that is, DMD patients with cardiac involvement.

In short, further investigation is needed to evaluate whether it is sustainable to use ARNi in DMD patients in order to improve quality of life and to assess the impact on long-term outcomes.

**Conclusions**

Our data suggest that the use of ARNi in DMD patients with DCM and an EF < 40% might be associated with an EF improvement. ARNi use may provide better quality of life (improved EF with a good tolerance of the medication) to these patients. Further studies are needed to investigate the impact on long-term survival.

**Conflict of interest**

None declared.

**References**

1. Guiraud S, Aartsma-Rus A, Vieira NM, Davies KE, van Ommen GJ, Kunkel LM. The pathogenesis and therapy of muscular dystrophies. *Annu Rev Genomics Hum Genet.* 2015; 16: 281–308.
2. D’Amario D, Gowran A, Canonico F, Castiglioni E, Rovina D, Santoro R, et al. Dystrophin cardiomyopathies: clinical management, molecular pathogenesis and evolution towards precision medicine. *J Clin Med.* 2018; 7: 291.
3. D’Amario D, Amodeo A, Adorisio R, Tiziano FD, Leone AM, Perri G, et al. A current approach to heart failure in Duchenne muscular dystrophy. *Heart.* 2017; 103: 1770–1779.
4. Kieny P, Chollet S, Delalande P, Le Fort M, Magot A, Pereon Y, et al. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. *Ann Phys Rehabil Med.* 2013; 56: 443–454.
5. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014; 371: 993–1004.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021; 42: 3599–3726.
7. Birnkranz DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol.* 2018; 17: 347–361.
8. Trucco F, Domingos JP, Tay CG, Ridout D, Maresh K, Munot P, et al. Cardiorespiratory progression over 5 years and role of corticosteroids in Duchenne muscular dystrophy: a single-site retrospective longitudinal study. *Chest.* 2020; 158: 1606–1616.
9. Villa C, Auerbach SR, Bansal N, Birnbaum BF, Conway J, Esteso P, et al. Current practices in treating cardiomyopathy and heart failure in Duchenne muscular dystrophy (DMD): understanding care practices in order to optimize DMD heart failure through ACTION. *Pediatr Cardiol.* 2022; 1-9.
10. Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years’ follow-up. *Am Heart J.* 2007; 154: 596–602.
11. 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: 136–140.
12. Schultz TI, Raucci FJ, Salloum FN. Cardiovascular disease in Duchenne muscular dystrophy: overview and insight into novel therapeutic targets. *JACC: Basic Transl Sci.* 2022.
13. Li JM, Chen H. Recurrent hypotension induced by sacubitril/valsartan in cardiomyopathy secondary to Duchenne muscular dystrophy: a case report. *World J Clin Cases.* 2019; 7: 4098–4105.