

Treatment of dystrophinopathic cardiomyopathy: review of the literature and personal results

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Cardiomyopathy is an almost universal finding in boys affected by Duchenne muscular dystrophy (DMD). Myocardial changes, as a result of the lack of dystrophin, consist of cell membrane degradation, interstitial inflammation, fatty replacement and fibrosis.

Dystrophinopathic cardiomyopathy generally starts as a preclinical or intermediate stage, with evolution toward advanced stages characterized by ventricle enlargement but also by symptoms and signs of heart failure (dyspnoea, peripheral edema and liver enlargement). However in few patients the dilation could be the first manifestation of the heart involvement.

The ability to detect overt cardiomyopathy increases with age, such that more than 80% of boys older than 18 years will have abnormal systolic function.

Several drugs have been employed with the aim to contrast the evolution of cardiomyopathy toward stages of severe congestive heart failure. A review of cardiac treatment in DMD and personal experience are reported and discussed.

Key words: Dystrophinopathic cardiomyopathy, deflazacort, ACE-inhibitors

Cardiac involvement in Duchenne muscular dystrophy (DMD) has long been recognized with initial pathology descriptions of myocyte hypertrophy and myocardial fibrosis, typical electrocardiographic abnormalities (1), and abnormal wall motion detected by early echocardiography (2, 3).

Dystrophinopathic cardiac involvement leads to a decline in cardiac function with age, resulting in ventricular dysfunction that contributes to early death from heart failure.

Cardiomyopathy in DMD generally starts as a preclinical or intermediate stage, with evolution toward advanced stages characterized by ventricle enlargement but

also by symptoms and signs of heart failure such as dyspnoea, peripheral edema and liver enlargement. Abnormalities on investigation are more common than symptomatic presentation. However in few patients the dilation could be the first manifestation of the heart involvement, caused by a diffuse disorganized fibrosis. The ability to detect overt cardiomyopathy increases with age, so that more than 80% of boys older than 18 years will have abnormal systolic function (4, 5).

No consensus exists regarding the proper pharmacologic intervention and timing of treatment for cardiomyopathy in patients with Duchenne muscular dystrophy. Corticosteroids have been reported to retard the development of left ventricular dysfunction in patients with DMD as measured by echocardiography and by cardiac magnetic resonance imaging (6). This is in contrast to findings in the mdx mouse model, where treatment with steroids resulted in hemodynamic deterioration, increased cardiac fibrosis, and increased sarcolemmal injury associated with tumor necrosis factor- α expression and in delta-sarcoglycan deficient cardiomyopathic hamster, where deflazacort is ineffective and may also have a negative impact on the cardiomyopathy rescue, possibly by boosting motor activity (7, 8). Others have hypothesized that interventions that benefit skeletal muscle may accelerate the development of cardiomyopathy because skeletal myopathy may limit cardiac demand secondary to decreased exercise capacity (9). Angiotensin-converting enzyme (ACE) inhibitors have been indicated in numerous studies as the first-line drugs in the management of patients with dilated cardiomyopathy and/or congestive heart failure, because they reduce both morbidity and mortality.

Several studies have demonstrated that the use of β -blockers (BBs) in patients with DMD reverse congestive heart failure signs and symptoms, delay progression of left ventricular dysfunction, and improve systolic function.

However, debate continues regarding the optimal timing of initiation of such treatments.

The purpose of this work is an update of the pharmacological treatment of dystrophinopathic cardiomyopathy combined with personal results.

Steroids treatment

In 2004, Manzur et al. (10) described the major findings of the Cochrane review regarding the results of five randomized controlled trials of the use of steroids in DMD. These trials presented evidence that use of daily prednisolone (0.75 mg/kg/day) or deflazacort (DFZ) (0.9 mg/kg/day) is able to increase strength in DMD with slightly different side effect profiles. Deflazacort appears to cause less weight gain and less bone mass deterioration, but more often it is associated with the development of asymptomatic cataracts. Long-term follow up of cohorts of patients treated under one or other of these drugs, and continuing the use of steroids beyond the loss of independent ambulation, showed that the increase in muscle strength was mirrored by improvement and possible preservation of cardiac function.

The first study examining the effects of deflazacort treatment on left ventricular cardiac function in DMD was published in 2003 by the group of D.W. Biggar (11). The study included 33 DMD patients, 21 of them taking DFZ for at least 3 years. The authors found that patients who have received DFZ for ≥ 3 years had a more preserved cardiac function than those who had not received the medication. In fact the prevalence of cardiomyopathy in the treated older patients was 5% compared with 58% in patients not treated. Preservation of cardiac muscle function was invariably associated with a better pulmonary and skeletal muscle function. Few and minor adverse effects were reported.

Two years later Markham et al. (12) published a retrospective cross-sectional study reviewing the echocardiograms of 111 Duchenne patients aged ≤ 21 years, in order to evaluate the effect of the steroid treatment on the natural history of cardiac function in DMD patients. Forty-eight out of 111 DMD patients had received steroids, prednisone [29] or DFZ [19]. Untreated and steroids-treated subjects did not differ in age, height, weight, body mass index, systolic and diastolic blood pressure or left ventricular mass. The shortening fraction (SF) was used as a marker of left ventricular dysfunction and considered normal if it was greater than

28%. The results showed that FS was lower in the untreated group than in steroid-treated group ($30\% \pm 7\%$ vs. $36\% \pm 5\%$; $p < 0.001$). Furthermore, in the second decade there was a dramatic increase in the number of boys – mainly those untreated – with demonstrable abnormalities in cardiac function.

Although this work did not satisfy the essential causal relationship criterion of temporality – cardiac evaluations were performed after steroid treatment – nevertheless it was the first study that compared the type of steroid and demonstrated the same beneficial effect on cardiac function with both drugs. The AA concluded that steroid therapy is able to modify the natural history of DMD.

The same work group performed a second study (13) in a smaller group [37] of DMD patients undergoing cardiac evaluation before and after steroid treatment. Furthermore they expanded the number of echocardiographic measures, including left ventricular wall stress (WS), contractility and the corrected velocity of circumferential fiber shortening (VCFc). The mean period of FU was 4.5 years and regarded 23 untreated and 14 treated DMD cases (mean age 7.5 ± 0.8 years, at the initial cardiac evaluation). The baseline echocardiographic measures did not differ in the two groups; however, at the final echocardiographic measure, DMD untreated boys had significantly larger left ventricular diastolic diameter (LVDD) and evidence of left ventricular dysfunction. The wall stress was higher and the contractility (VCFc) less yielding a negative stress velocity relationship (VCFdiff). The frequency of ventricular dysfunction increased significantly with age for untreated cases. On the other hand, steroids treated DMD patients did not have a significant change in functional indices compared to baseline. At the time of the final evaluation, only 2 treated cases vs. 16 untreated had evidence of ventricular dysfunction ($p < 0.001$).

ACE-inhibitors treatment

Angiotensin-converting enzyme inhibitors (ACEIs) are a group of pharmaceuticals primarily used in treatment of hypertension and congestive heart failure. ACE inhibitors block the conversion of angiotensin I to angiotensin II. They therefore lower arteriolar resistance and increase venous capacity, increase cardiac output and cardiac index, stroke work and volume, lower reno-vascular resistance and lead to increased natriuresis.

ACE inhibitors can be divided into three groups based on their molecular structures:

1. Sulphydril-containing agents;
2. Dicarboxylate-containing agents;
3. Phosphonate-containing agents.

The first group includes Captopril – the first ACE inhibitor – and Zofenopril.

The second group – the largest one – includes Enalapril, Ramipril, Quinapril, Perindopril, Lisinopril and Benazepril. Fosinopril is the only member of the third group.

Treatment with ACEIs has been shown to reduce mortality and hospitalization in patients with systolic heart failure or heart failure with reduced ejection fraction (14, 15). Furthermore a prophylactic effect of ACE-inhibitors has been reported in Syrian hamster cardiomyopathy, an experimental model of delta-sarcoglycanopathy, phenotypically similar to DMD (16, 17).

Perindopril

In 2005, the group of Duboc in France (18) reported the results of a phase I three-year multicenter, randomised, double-blind trial of the ACEIs perindopril (2 to 4 mg/day) in a group of 57 DMD patients, aged 10.7 ± 1.2 years, with normal ejection fraction (group 1) vs. placebo (group 2). In phase II, all patients received open-label perindopril for 24 more months. Left ventricular ejection fraction (LVEF) was measured at 0, 36 and 60 months. At the end of phase I, mean LVEF was $60.7 \pm 7.6\%$ in group 1 vs. $64.4 \pm 9.8\%$ in group 2 and it was $< 45\%$ in a single patient in each group ($p = \text{NS}$). At 60 months, LVEF was $58.6 \pm 8.1\%$ in group 1 vs. $56.0 \pm 15.5\%$ in group 2 ($p = \text{NS}$). A single patient had an LVEF $< 45\%$ in group 1 vs. 8 patients in group 2 ($p = 0.02$). The authors concluded that early treatment with perindopril over 60 months delayed the onset and progression of left ventricular dysfunction in children with DMD. This paper received some criticism by Claudia Stollberger and Josef Finsterer from Vienna, concerning the study design and conclusions.

Two years later, the same group published a second paper on perindopril, reporting the results on the survival of the patients enrolled in the previous study, after extended follow up to 10 years (19). They documented a survival benefit conferred by the early, instead of delayed, administration of perindopril in patients with DMD between the ages of 9.5 and 13 years, presenting with normal LVEF at entry in the study. The effect of treatment on survival seemed to have begun at 7 years, beyond which mortality continued to increase in the group of patients who did not receive early perindopril therapy, reaching a difference statistically significant at 10 years follow up.

Enalapril

In 2006, Ramaciotti et al. (20) described the response to enalapril and its relation to dystrophin mutation type, ventricular size, or age at the onset of left ventricular

systolic dysfunction. To this purpose they retrospectively reviewed serial clinical and echocardiographic data from 50 DMD patients, age 10-20 years. The median follow up was 53 months (range 8-96 months). Twenty-seven patients (54%) maintained normal left ventricular (LV) function, whereas 23 (46%) developed systolic dysfunction. The mean age at the onset of LV systolic dysfunction was 13.2 ± 2.4 years. Among patients who developed LV systolic dysfunction, 10 (43%) showed normalization of shortening fraction (responders) whereas 13 (57%) were not responders. No specific mutation was associated with the response to enalapril or was predictive of the development of LV systolic dysfunction.

Recently, the effects of an early treatment with enalapril i.p. (1 to 5 mg/kg for 4-8 weeks) on the pathology signs of exercised mdx mouse model have been studied and compared with those of 1 mg/kg alfa-methylprednisolone (PDN), as positive control (21). Enalapril caused a dose-dependent increase in fore limb strength, the highest dose leading to a recovery score similar to that observed with PDN. A dose-dependent reduction of superoxide anion production was observed by di-hydroethidium staining in tibialis anterior muscle of enalapril-treated mice, approaching the effect observed with PDN. In parallel, a significant reduction of the activated form of the pro-inflammatory Nuclear Factor- κ B has been observed in gastrocnemius muscle. The results suggest the ability of enalapril to blunt angiotensin-II dependent activation of pro-inflammatory and pro-oxidant pathways which may be earlier events with respect to the pro-fibrotic ones, and may in part account for both functional impairment and muscle necrosis.

Angiotensin II receptor antagonists

Angiotensin II receptor antagonists (ARBs) have very similar effects to angiotensin converting enzyme inhibitors and are used for the same indications (hypertension, heart failure, post-myocardial infarction). Their mechanism of action, however, is very different. ARBs are receptor antagonists that block type 1 angiotensin II (AT1) receptors on blood vessels and other tissues such as the heart. ARBs are primarily used where patients are intolerant of ACE inhibitor therapy. They do not inhibit the breakdown of bradykinin or other kinins, and are thus only rarely associated with persistent dry cough and/or angioedema, that limit ACEi therapy. More recently they have been used for the treatment of heart failure. Losartan, irbesartan, olmesartan, candesartan, valsartan and telmisartan are included in this group of drugs.

Losartan

Two papers (22, 23) have recently been published stressing as chronic losartan administration is able to preserve or improve cardiac function in dystrophin-deficient mdx mice, by a decrease of cardiac and skeletal muscle fibrosis. Nevertheless no impact on the skeletal muscle disease progression was observed, suggesting that other pathways that trigger fibrosis dominate over angiotensin II in skeletal muscle long term, unlike the situation in the heart. These studies suggest that ARBs may be an important prophylactic treatment for DMD-associated cardiomyopathy, but they will not impact skeletal muscle disease.

Beta-blockers

Beta-blockers are drugs that bind to beta-adrenoceptors and thereby block the binding of norepinephrine and epinephrine to these receptors, with consequent inhibition of normal sympathetic effects that act through these receptors. Therefore, beta-blockers are sympatholytic drugs. The first generation of beta-blockers were non-selective, meaning that they blocked both beta-1 (β_1) and beta-2 (β_2) adrenoceptors. Second generation beta-blockers are more cardioselective in that they are relatively selective for β_1 adrenoceptors. Beta-blockers bind to beta-adrenoceptors located in cardiac nodal tissue, the conducting system, and contracting myocytes. The heart has both β_1 and β_2 adrenoceptors, although the predominant receptor type in number and function is β_1 . Beta-blockers are able to reduce sympathetic influences that normally stimulate chronotropy (heart rate), inotropy (contractility), dromotropy (electrical conduction) and lusitropy (relaxation). Therefore, beta-blockers cause decreases in heart rate, contractility, conduction velocity, and relaxation rate.

Carvedilol

Although several studies have shown carvedilol to be an effective therapy for patients with other form of dilated cardiomyopathy, children and adolescents included (24) few data exist concerning its safety and efficacy for patients with muscular dystrophy.

In 2001, Saito et al. (25) evaluate the efficacy of oral carvedilol (10.1-40.3 $\mu\text{g}/\text{kg}/\text{day}$) for 6 months in 4 DMD patients who had elevated plasma atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP), and a low ejection fraction ($\text{EF} < 40\%$) in echocardiography. The values did not change significantly compared with controls. Clinical symptoms also did not change in either group. They conclude that carvedilol therapy did not change the left ventricular dysfunction in DMD. However carvedilol

therapy can be safe for patients with dilated cardiomyopathy associated with muscular dystrophy, even producing a modest improvement in systolic and diastolic function (26).

Combination of therapy

It has been reported that the combination of an ACE-inhibitor and a beta-blocker has additive effects in patients with congestive heart failure. Such an approach has been extended to Duchenne muscular dystrophy patients with left ventricular dysfunction in order to assess whether this combination was associated with long term survival of DMD patients with dilated cardiomyopathy.

In 1999, Ishikawa et al. (27) reported the effectiveness of the combination of ACEI and beta-blockers in 11 DMD patients with symptomatic heart failure for relief of symptoms and decrease of activated neuroendocrine level during 5-year follow up.

In 2006, Kajimoto et al. (28) confirmed the beneficial effects of the association beta-blocker carvedilol/ACEI on ventricular function in 13 patients with muscular dystrophy compared with the ACEI only. In fact the combination therapy of carvedilol and an ACEI for 2 years resulted in a significant increase in left ventricular fractional shortening (LVFS), while in the ACEI group, there was no significant change in LVFS. Left ventricular end-diastolic dimension increased in the ACEI group, but not in the carvedilol/ACEI group.

Ten years later, Ogata et al. (29) studied the long term efficacy of an ACEI and a beta-blocker in 52 DMD patients with reduced LVEF, with [12] or without [40] symptoms of heart failure. They showed that 5-year and 7-year survival rates of symptomatic patients were 81 and 71% respectively. Survival rate became 0 at 10,9 years. In the prevention group (asymptomatic patients) 5- and 7-year survival rates were 97 and 84% respectively, and 10-year survival rate was 72%.

The beneficial effects of the combined ACEIs and beta-blockers therapy has been observed in DMD patients, with both gene deletions or point-mutations (30).

Recent papers (31, 32) confirm that the use of ACEIs and beta-blockers in patients with DMD reverse congestive heart failure signs and symptoms, delay regression of left ventricular dysfunction and improve systolic function.

In conclusion it seems that ACEIs and Beta-blockers may delay the onset and the progression of cardiac dysfunction, have to be recommended earlier in this disease and should become the "gold standard" for the treatment of dystrophinopathic cardiomyopathy. However no consensus remains regarding the timing of treatment.

Personal experience

Our work group has constantly focused attention to the myocardial involvement in DMD. A compendium of the results obtained in the field can be found in Engel & Franzini-Armstrong's textbook "Myology" (5).

The therapeutic approach of cardiomyopathy has only recently been accepted and is based on the use of ACE inhibitors and beta-blockers to prevent cardiac function deterioration. Digitalis, diuretics and anticoagulants are used in the acute phases, such as congestive heart failure episodes.

We are convinced that the therapeutics are more effective when administered very early in the course of disease – please remember the latin saying "to prevent is better than to cure" – before the fibrosis is established. Dystrophin plays a critical role in the myocardium by connecting the cytoskeleton to the external membrane, so that its absence causes membrane fragility, loss of transductional force and myocyte necrosis, promoted by mechanical stress (33, 34). The efficacy and the progressive benefit over time of ACEis are consistent with a hemodynamic effect and/or a specific antifibrotic effect of this class of drugs and are concordant with experimental observations made in animal models (35, 36). Long-term therapy with DFZ is also effective in slowing down the progression of fibrosis in the dystrophin deficient heart.

Our group adopted deflazacort in the treatment of DMD boys since 1990. In 2004 we published (37) in cooperation with the Toronto group the results of a prolonged observation on 69 DMD patients, treated for at

least 4 years by two different treatment protocols (0.6 mg/kg/day, 20 days on/10 days off [N-Protocol] vs. 0.9 mg/kg/day [T-Protocol]) comparing both the long-term benefits and side effects. With respect to the group of 49 untreated DMD boys, the report illustrated the long-term beneficial effects on muscle function and motor performance of deflazacort treatment in both protocols. However the high dose protocol (T-protocol) seemed to be more effective but frequently associated with asymptomatic cataracts.

In the same year we presented at the Mediterranean Society of Myology Congress the results on cardiac function of a long-term period of observation of 60 DMD boys treated with DFZ at the dosage of 0.6 mg/kg/day for 20 days/month (38). The mean age at the enrollment was 5.6 years (range 4-11.7); the follow up was 83.7 months on average (range 36-144 months). All the patients had a fourth-month cardiac evaluation by ECG and echocardiography. The following parameters were evaluated: PQ interval, PQ segment, QT interval, QT dispersion, Cardiomyopathic Index (QT/PQ, adjusted for HR), presence of Arrhythmias or Blocks, presence of T wave anomalies, by the ECG; four chambers dimension, wall thicknesses, Ejection Fraction, Fractional Shortening, ultrasonic integrated backscatter (IBS), by the echocardiogram.

At the enrollment, 7 patients had a normal heart, 50 presented a pre-symptomatic stage and 3 were in the arrhythmogenic stage (5). At the end of the study, no change in electrocardiographic and echocardiographic parameters were observed (Tables 1 and 2). Two patients

Table 1. DFZ treatment. ECG parameters.

	At the starting of DFZ treatment	At the end of DFZ treatment	P value
Heart rate	90.9 ± 12.3	77.9 ± 14.7	0.47
PQi	11.5 ± 1.7	12.5 ± 1.8	0.88
PQs	3.2 ± 1.4	2.7 ± 0.9	0.24
QT	33.2 ± 2.4	35.4 ± 3.0	0.92
CM Index	4.9 ± 1.2	5.2 ± 1.2	0.10

Table 2. DFZ treatment. Echocardiographic parameters.

	At the starting of DFZ treatment	At the end of DFZ treatment	P value
LVEDD	42.4 ± 5.7	44.1 ± 4.8	0.00
LVESD	27.4 ± 4.7	28.7 ± 4.3	0.00
LVEDV	82.8 ± 30.7	89.8 ± 26.9	0.00
LVESV	29.3 ± 16.0	32.6 ± 15.2	0.00
SV	53.5 ± 15.4	57.0 ± 13.0	0.03
LVEF	65.7 ± 4.2	64.4 ± 4.5	0.06
FS	36.0 ± 2.8	35.0 ± 3.2	0.06
IVS	7.3 ± 1.0	8.0 ± 1.2	0.00
LPFW	8.1 ± 1.3	8.6 ± 1.0	0.00

shifted from a normal heart to the a presymptomatic stage due to a pathological increase in Cardiomyopathic Index, while 2 passed from the presymptomatic stage to the spotty fibrosis stage. None of them presented with overt cardiomyopathy. The data above shown suggest that treatment with deflazacort is able to preserve cardiac function in Duchenne patients.

In 2010, on the occasion of the XII ICNMD, we reported the results of a long-term administration (10,8 years on average) of fasinopril and deflazacort in 52 DMD patients aged 18-34,1 years in order to assess whether the early and prolonged administration of both drugs was able to prevent or delay the onset of an overt dystrophinopathic cardiomyopathy (39). The dosage of fasinopril was 0.3mg/kg b.i.d. continuously. Mean age at the onset of fasinopril administration was 11,4 years (range 6-19). All the patients have been examined at 4-month intervals using a standardised clinical protocol, including clinical examination, standard and dynamic ECG, M-Mode and 2D echocardiography, Echo-color-Doppler-cardiography. We considered as the onset of an overt cardiomyopathy a value of ejection fraction, evaluated in 2D echo-cardiography, $\leq 50\%$. A historical group of 35 DMD patients – drug naïf – served as control. A LVEF $> 50\%$ was observed in 76,9% of DMD treated patients, at a mean age of 23 years, vs 15% of DMD patients of the control group ($p < 0,001$). On the other hand a LVEF $< 50\%$ was observed in 23,1% of DMD treated patients, at a mean age of 19,4 years, vs 85% of the control group, at the same age ($p < 0,001$). Kaplan-Meyer freedom cardiomyopathy was 70% at the age of 23 years in DMD treated boys vs 15% in the control group.

The effects of steroids and ACEIs on cardiac function in DMD boys have not be recently confirmed (40). However the study presents several limitations, such as the study design based on physician preference, older boys on combination treatment while younger on steroids alone, too short period of follow up.

In conclusion, we can affirm that:

- Steroids in general and deflazacort in particular, remain the “gold standard” for the treatment of Duchenne muscular dystrophy (41) as they are able to modify the natural history of DMD.
- ACE inhibitors alone and/or in association with deflazacort are effective in slowing down the onset and the progression of dystrophinopathic cardiomyopathy.
- Beta-blockers are useful in DMD cases to reduce heart rate.
- Cardiological treatment should start very early (5 years of age) in the course of the disease, before the fibrosis is established.

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