Chapter

Cardiomyopathy in Duchenne Muscular Distrophy: Clinical Insights and Therapeutic Implications

Rachele Adorisio, Erica Mencarelli, Nicoletta Cantarutti and Maria Grandinetti

Abstract

Duchenne muscular dystrophy cardiomyopathy (DMD-DCM) is characterized by progressive ventricular dilation and dysfunction that can begin at any age and worsens over time. Thanks to the lengthening of life expectancy due to better management of respiratory involvement, end-stage heart failure (HF) is becoming the main cause of death for DMD patients. Therefore, from the time of DMD diagnosis, every effort should be focused to early detect the onset and the worsening of the DMD-DCM, with the aim of starting and modulating the therapy to slow the progression of cardiac dysfunction. In cardiac evaluation, biomarkers, electrocardiograms, and echocardiograms must be considered, but cardiac magnetic resonance (CMR) is now acquiring a leading role due to its sensitivity in the earlier identification of cardiac involvement. The management of DMD-DCM at end stage is a difficult challenge that requires a multidisciplinary team composed of clinical cardiologists, electrophysiologists, cardiac surgeons, neuromuscular specialists, and psychologists. Because of the lack of specific drugs for DMD, we will review the actual cardiovascular armamentarium including drugs used for HF.

Keywords: duchenne muscular dystrophy, DMD, dilated cardiomyopathy, neuromuscular disease, dystrophin, heart failure

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked degenerative neuromuscular disease that affects the skeletal muscles and the heart and over time leads to loss of walking, severe respiratory complications and progressive cardiac dilation and dysfunction.

It is caused by a mutation of the DMD gene, the largest gene in the human genome, mapped on the X-chromosome that codes for dystrophin, an essential protein for the stability of the myocyte membranes. The type of mutation and the degree of reduced expression of this structural protein influences the degree of muscle and cardiac impairment and especially the speed of myopathy progression. The milder forms are generally identified with the term Becker's muscular

dystrophy (BMD) while the most severe and rapidly evolving forms, due to a severe reduction or total absence of dystrophin, are properly defined as DMD. Due to the X-linked recessive inheritance, the condition of female carriers must also be considered; they have a second normally functioning allele of dystrophin gene, thus they are generally characterized by a completely normal muscular and cardiac phenotype but may also present a mild/variable expression of the disease [1].

The incidence of DMD is approximately 1 in 5000 live male births, with 2/3 of the cases due to the transmission of the X-chromosome containing the mutated gene from a carrier female to male offspring and the remaining 1/3 of cases consequent to de novo mutations.

Generally the first manifestation of the DMD is muscle weakness that begins around the age of four and worsens quickly, leading to the loss of independent walking by the age of ten and to respiratory dysfunction around the second decade of life. The cardiac involvement begins around 6–10 years of age [2, 3] while cardiovascular symptoms are rare before the age of twenty and often appear when the degree of cardiac dysfunction is severe [4].

In last decades, the life expectancy of patients with DMD has grown considerably as a result of advances in the prevention and management of respiratory complications. As a result, there has been a significant increase in manifestations of advanced cardiomyopathy that is becoming the main cause of morbidity and mortality for these patients. This has led to a growing interest in the prevention and management of DMD-DCM [5–7].

While some aspects of DMD-DCM assessment and therapy are well defined by current guidelines [8], such as the need of routine cardiac evaluation and the indication to start prophylactic cardio-protective therapy from the age of ten in all patients, many other aspects remain under investigation, especially at end stage phase.

2. Genetic basis and pathophysiology of DMD-DCM

The DMD gene, encoded on the X chromosome, is the longest gene of our genome; it contains long introns with many "hotspots" susceptible to a high rate of mutations which can lead to the deletion (60–65% of all DMD mutations) or duplication (10%) of one or many exons. Shorter mutations such as point mutations are responsible for the remaining 25% of DMD cases. One third of DMD cases are due to de novo mutations while two third are inherited. The mutations resulting in the production of a truncated protein or of a dystrophin lacking in structural domains necessary for interaction with other proteins, are responsible for the most severe forms of the disease [9].

Dystrophin is a long intracellular protein of 3685 aminoacids and a molecular weight of 427 kDa. It is composed by four domains: an *amino-terminal domain* that interacts with actin of the myocyte cytoskeleton, a *central rod-like domain* that contains sites of interaction with anionic lipids and with neural NOS, a second actin-binding motif and four short proline-rich spacers responsible of the elasticity of the protein, *a cysteine-rich domain* that provides the protein–protein interaction and stabilizes dystroglycan binding, and a *C-terminal domain*, that interacts with several cytoplasmic, integral membrane and extracellular glycoproteins to create a protein complex called DAPC (dystrophin-associated protein complex) (**Figure 1**). The DAPC, in healthy myocytes, anchors the cytoskeleton and the plasma membrane to the extracellular matrix, ensuring stability and resistance to cells during contractions [9]. The lack of dystrophin, or the presence of an abnormal dystrophin, causes the loss of stability of this complex connection system with consequent greater
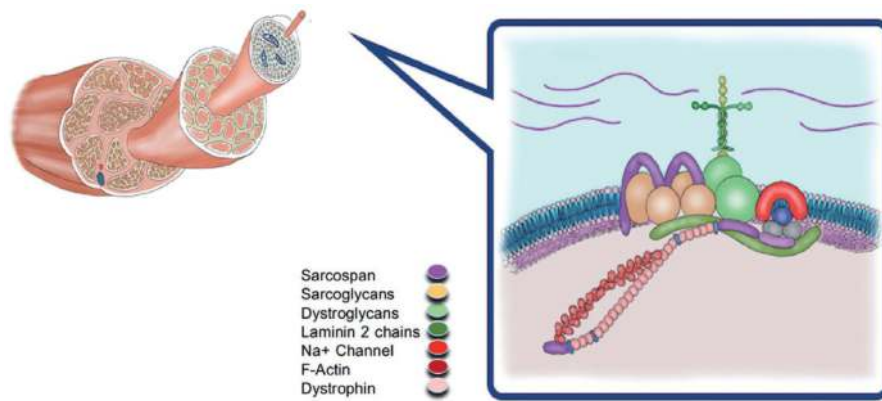
Figure 1.
The dystrophin- associated protein complex (DAPC). Dystrophin and DAPC plays an essential structural role in linking the actin of cytoskeleton to the extracellular matrix. The subunits of the DAPC, such as the sarcoglycans, have a vital role in the maintenance of muscle integrity. Dystrophin, a flexible rod-like cytoplasmic protein, directly interacts with the actin polymers of the cytoskeleton and with a complex of transmembrane glico-proteins composed by sarcoglycans, beta- and alpha-dystroglycan that creates a connection with the extracellular matrix by its linking with laminin-2.

fragility of the cell membrane of myocytes, dysregulation of cellular signaling and high susceptibility to damage and cell death. Cellular stress and cardiomyocyte death cause the release of cytokines, chemokines and cellular debris that attract neutrophils, macrophages and, later in time, fibroblasts. This process leads to the replacement of the heart muscle with fibrous tissue; it generally starts from the region behind the posterior mitral valve apparatus and proceeds toward the ventricular apex and around the heart, and from the epicardium to the endocardium, to lead, ultimately, to the dilation and the dysfunction of the ventricles [10]. In this scenario, inflammation, dysregulation of the intracellular calcium (Ca2+) signaling, alteration of synthesis of nitric oxide, inadequate anti-oxidant response, mitochondrial malfunction and deficiency of membrane repair systems are all mechanisms involved in the molecular pathogenesis of DMD-DCM and they can be addressed for the development of new disease-modifier therapies [11].

Fibrosis, abnormal Ca2+ homeostasis and elevated reactive oxygen species are also predisposing factor to the onset of ventricular arrhythmias in DMD-DCM. Recently, a predisposition to pacing induced ventricular arrhythmias was demonstrated in an animal model of DMD. In this model, the aberrant Ca2+ release through RyR2, which leads to delayed after depolarizations (DADs) and triggered ventricular arrhythmias, was related to the oxidated Ca2+/calmodulin-dependent protein kinase II, Ox-CaMKII. Genetic inhibition of Ox-CaMKII normalized intracellular Ca2+ and prevented ventricular arrhythmias in this model [12]. Another interesting study suggested that arrhythmias could also result from an alteration of the components of the cardiac gap junction; in particular it has been proposed that the dislocation and anomalous S-nitrosylation of connexin 43 (Cx43) lead to the early depolarization of the cytoplasmic membrane and the consequent generation of action potentials. Then, these channels can be therapeutic targets to prevent fatal arrhythmias in patients with DMD [13].

3. Clinical course

The diagnosis of DMD may occur around 4 yo for difficulty in gait, calf hypertrophy, delayed speech, inability to jump or stand without using the arms for assistance (Gower maneuver), toe walking and difficulty in climbing stairs.

Over the time the progressive muscle waste leads to loss of ambulatory capacity and to decline of respiratory and cardiac functions [14].

Literature reports the beginning of ongoing cardiac disease processes as around 6–10 years of age. Echocardiographic abnormalities and clinical DCM can occur at any age but often appear around 14–15 yo and are common over 18 years of age [15]. Symptoms are mild or completely absent up to the most advanced stages of cardiomyopathy, and this is mainly due to the significant reduction in oxygen consumption and in energy expenditure consequent to muscle weakness. It is remarkable that often the severity of cardiomyopathy does not correlate with the degree of skeletal muscle weakness, thus regular cardiac evaluation is very important also in patients with mild motility impairment and it is required before any invasive diagnostic procedure or surgery.

In the last decade, the increase in life expectancy, deriving from the better management of the respiratory involvement and the improved supportive cares, have resulted in a sharp increase in the number of patients with severe cardiomyopathy, and to date, end-stage HF has becoming one of the leading causes of morbidity and mortality in DMD [6].

Data from a multicentre Pediatric Cardiomyopathy Registry (PCMR) show a high prevalence of DCM also in milder forms of dystrophinopathies as in BMD (up to 90% of cases). Interestingly, in these patients, detection of cardiomyopathy often occurs at a more advanced stage and the progression of the LV dysfunction and dilation may be more rapid than in patients with DMD. Despite this, mortality rate for DMD patients with DCM is significantly worse than that of BMD patients, who can undergo heart transplant [16].

4. Noninvasive assessing of DMD-DCM

From the time of DMD diagnosis, every effort should be focused to detect early the onset and the progression of DCM. Early recognition and periodic re-evaluation are essential to guide therapy and to identify patients at increased risk of progression of cardiomyopathy and major cardiac events. Clinical evaluation remains challenging because most of these patients have often low blood pressure values and cool extremities because of reduced skeletal muscular mass even in the presence of hemodynamic compensation. Therefore, multiparametric evaluation is crucial to correctly recognize the progression of cardiac impairment [8].

4.1 Cardiovascular biomarkers

Serum biomarkers are often very useful for the diagnosis and monitoring heart disease. In particular, serum levels of cardiac troponin I/T are known to be associated to the extension of myocardial damage, but there are conflicting results about their diagnostic and prognostic implications in the DMD-DCM. Actually, only troponin I showed to be reliable in patients with neuromuscular disorder [17]. Troponin I levels seem to be significantly elevated in patients with initial myocardial fibrosis expressed by mild late gadolinium enhancement (LGE) at the cardiac magnetic resonance (CMR) compared to those without LGE. Interestingly, this positive association between troponin levels and myocardial fibrosis is lost when LGE degree becomes moderate-to-severe, probably because at advanced stage of cardiomyopathy most of myocardium is already substituted by fibro-fatty tissue, therefore the release of myocardio-necrosis enzymes is reduced [18].

Natriuretic peptides are well established markers of HF and congestion in DCM. In DMD, pulmonary hypertension caused by impairment of the respiratory muscles

and restrictive physiopathology are considered to be involved in the mechanism of increased values of plasma natriuretic peptide. In addition to the more commonly used brain natriuretic peptide (BNP), a significant elevation in plasma alpha-atrial natriuretic peptide (alphaANP) levels is found as a sign of a poor prognosis and may be a useful index for the management of patients with DMD-DCM [19].

In the management of HF is very important to assess renal function. In DMD serum creatinine values are generally very low as a consequence of their reduced muscle mass and therefore creatinine cannot be considered a good marker of renal function. In these patients, serum values of cystatin C, a protein produced by all cells, not only by muscle cells, are a good parameter for assessing renal function, because they better correlate with glomerular filtration rate (GFR) and cardiac dysfunction. Furthermore, it is reported a significant correlation between Cystatin C and cardiac dysfunction, providing for the first time a novel marker to identify cardio-renal syndrome in patients with DMD [20].

4.2 Electrocardiography and cardiac imaging

Electrocardiogram and transthoracic echocardiogram are the two fundamental exams advised to establish baseline cardiac involvement and they are recommended annually in all patients since the diagnosis of DMD. After the age of ten, cardiac assessment should have been *at least* yearly because of the increased risk of DCM. Even in the absence of abnormalities on the echocardiogram, a CMR should be performed in all children without contraindications from 7 years of age, when it is possible to perform this examination without the need for anesthesia, with the aim to detect early any regional dysfunction or myocardial fibrosis. When some abnormalities are found, controls should be more frequent [8].

Electrocardiographic (EKG) changes are very common (up to 90%). Initially, myocardial dystrophy may manifest itself as mild nonspecific EKG changes such as increased R-wave voltage in right or left precordial leads, QRS fragmentation, or slight alterations in ventricular repolarization. When cardiac disease is overt, R-wave voltage decreases and abnormal Q waves may appear generally in infero-lateral leads. ECG often shows also one of the following features: right axis deviation, conduction defects or short PR intervals, polyphasic R waves in V1, right bundle branch block, flat and inverted T waves, and prolonged heart rate-corrected QT interval. Sinus tachycardia is very common in DMD and, together with the reduction of circadian index and the scarce heart rate variability, it is a sign of the autonomic dysfunction that often affect these patients. 24-hours ECG monitoring is essential to detect autonomic dysfunction and it is recommended in case of suspect of arrhythmias and for routine monitoring of advanced stage of DMD-DCM, in which the presence of atrial fibrillation, atrial or ventricular arrhythmias may affect prognosis and change the management [21].

Echocardiography allows to identify the *LV dilation*, defined in children by a LV end-diastolic diameter that exceeds the mean value expected for age and sex by two standard deviations, and *LV systolic dysfunction*, defined by a LV ejection fraction (LVEF) <55% or a fractional shortening (FS) <28% [22]. Despite the advances in 2D and 3D techniques, FS is still considered the best surrogate of LV systolic function, among the echocardiographic possibilities, for its high reproducibility and its strong correlation with CMR LVEF [23]. Furthermore, routinely recognition of diastolic dysfunction is important because it is very frequent in all stages of DCM and can precede contractile impairment.

For earlier detection of LV impairment, speckle tracking echocardiography is also very useful, as it is a technique able to evaluate subclinical LV dysfunction before development of overt LVEF reduction. Global longitudinal strain (GLS), obtained by

2D speckle tracking echocardiography is abnormal in nearly 50% of DMD patients with a normal LVEF, and a decrease of 0,34% per year of GLS in DMD patients according to age has been recently reported [24]. The lowest values of strain is often observed in the inferolateral and anterolateral mid-basal segments. However, speckle tracking analysis is often limited in DMD because echocardiographic image quality is poor in these patients and declines by 2,5% for each 1 year increase in age because of chest deformities, lung hyperinflation, and limited mobility [25].

CMR is becoming the gold standard exam in the evaluation of DMD-DCM, especially because it allows a non-invasive myocardial tissue characterization by LGE and T1 mapping techniques, using non –ionizing radiations. It also offers the possibility to better analyze the size and global and regional kinetics of the left and right ventricles, not being limited by body habitus and providing a more accurate and reproducible three-dimensional views if compared to echocardiography. LGE identifies fibrosis, it may have a subepicardial or transmural distribution, it is often initially localized in the inferolateral wall, and its extension allows to stratify the severity of cardiac involvement. LGE is an independent predictor of adverse cardiac events in DMD patients, also in those with a preserved LVEF [26]. T1 mapping technique pre- and post-contrast is able to identify diffuse fibrosis even earlier than LGE but T1 mapping value varies a lot depending on the sequence used, and it cannot discriminate diffuse myocardial fibrosis from inflammation or fat infiltration [27]. Finally, CMR can also provide myocardial strain analysis, using feature-tracking technique.

CMR can be useful also to evaluate more precisely the severity of myocardial dysfunction and fibrosis in further stages, to assess the efficacy of anti-remodeling therapy, to screen asymptomatic DMD female carriers. However, the high costs, patient's claustrophobia and the technical difficulties to obtain the exam in patients with home ventilator may limit its use in this group of patients.

## 5. Management of DMD-DCM from prevention to end-stage HF

In the clinical course of DMD-DCM three stages of DCM can be distinguished: a *pre-clinical stage*, a *clinical stage* and an *end-stage DCM* (**Figure 2**).

The *pre-clinical stage* is characterized by normal dimension and function of the heart. It usually limited to the early teenager years of life. In this phase, although the LV contractile function is preserved (LVEF>55%), the process of myocyte damage and fibrotic myocardial replacement has generally already begun and it can manifest itself with nonspecific EKG changes, subtle local wall motion abnormalities, diastolic dysfunction consequent to cardiomyocyte hypertrophy, reduction in ventricular strain values and LGE at CMR.

At this stage of the DMD-DCM, the aim will be to delay the onset of ventricular contractile dysfunction. Current recommendation advices to start angiotensin converting enzyme inhibitor (ACE- I) as preventive strategy. Perindopril 2–4 mg/die, [28] or an angiotensin receptor blocker (ARB) can be prescribed in all DMD patients from the age of ten. The indication to start therapy earlier, in patients with initial signs of cardiac involvement (such as the presence of mild LGE) but with preserved contractile function is still under debate and investigation [8].

At this early phase of DCM, when LV is mildly dilated, the use of mineralo-corticoid receptor antagonist (MRA), such as eplerenone or spironolactone, may slow the rate of decline of LV function. Further studies are needed to determine the effect of combined cardioprotective therapy on event-free survival in these patients [29, 30].

The *clinical stage* includes a wide range of patients, with various degree of LV dilation and dysfunction, without any symptoms or with initial signs or symptoms
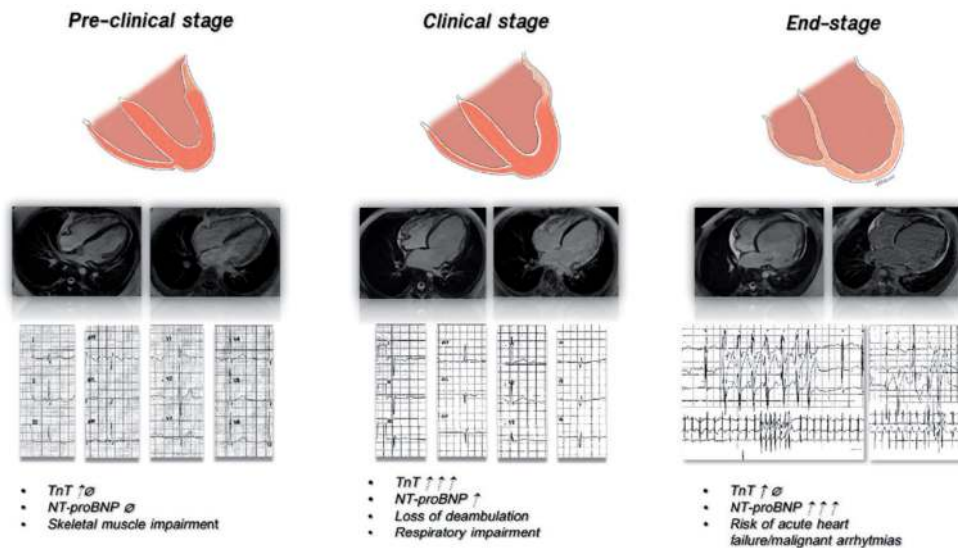
Figure 2.
Cardiac magnetic resonance (CMR), electrocardiographic (EKG) features and clinical status at different stages of the DMD-DCM progression. In the pre-clinical stage left ventricular (LV) function is still preserved, CMR may identify initial fibrosis, at the EKG some alterations such as QRS fragmentation, rsr' complexes in V1 and alterations of ventricular repolarization may appear, and blood levels of troponin T (TnT) may be slightly or moderately high while NTproBNP is normal. The clinical stage is characterized by a certain degree of LV dysfunction and dilation, inflammation and fibrotic replacement of the heart muscle are extended, as shown by the wide distribution of late gadolinium enhancement (LGE) areas at CMR imagines, abnormal Q waves appear at the ECG, and the values of TnT and NTpro BNP are usually very high and moderately high respectively. In the end-stage, LV dilation and dysfunction are severe, much of the heart muscle is replaced by fibrous tissue, filling pressure increases, and episodes of acute heart failure and ventricular arrhythmias become frequent, NTproBNP values are very high while TnT values may not be particularly high due to reduced total cardiac muscle mass.

of HF. This phase can start at any age but frequently it begins after the age of ten. Few studies have focused on treating DMD patients with mild to moderate LV systolic dysfunction (LVEF>30% <50%), and the current consensus statement supports the use of traditional treatment for HF to treat the progression of DCM. All patients with at least mild ventricular dysfunction should be treated with an ACE-I or an ARB. In particular lisinopril (ACE-I) and losartan (ARB) have shown equal effectiveness in preserving or improving ventricular function in established DCM [31]. Due to their ability to reduce the fibrotic process and stabilize LV systolic function, MRAs should be considered in this phase of DMD-DCM, even in case of mild reduction of LVEF, that is much earlier than indicated by current guidelines for the management of HF (symptomatic patients with LVEF <35%). In addition, a beta blockers (BB) such as carvedilol, is indicated when a sufficient improvement in cardiac function is not achieved with the initial therapy with ACE-I/ARB. Routine use of the BBs in DMD patients has been controversial in the past years due to conflicting results on their efficacy obtained from retrospective and non-randomized prospective studies. Nowadays, the superiority of combination therapy with an ACE-I/ARB and a BB over monotherapy with ACE-I/ARB is supported by studies that have shown more beneficial effect on LV function, on prevention of major cardiac events (death, deterioration of HF and severe arrhythmias) and on long-term survival [32–34]. Furthermore, in DMD-DCM, BBs are also useful to control sinus tachycardia caused by autonomic dysfunction and other forms of tachyarrhythmia.

The *end-stage* DCM is characterized by severe degree of LV dysfunction (LVEF <30%) and dilation, the patients might have signs and/or symptoms of HF. Also, they may have rhythm disturbances, with a higher risk of acute decompensation of HF and sudden cardiac death. Generally this phase occurs after the age of twenty

but in some more aggressive forms of CMD it can manifest earlier. At this stage of disease every effort must be aimed to reduce acute events and hospitalizations and to improve symptoms and quality of life of these patients. Medical treatment includes a combination of an ACE-I/ARB, an MRA and a BB at the maximum tolerated or recommended dose, according to European and American Guidelines for the management of HF [35, 36]. Based on recent evidence of the efficacy of the heart rate reduction strategy in lowering the long term incidence of acute adverse events in DMD patients with advanced cardiac involvement, ivabradine should be considered if LVEF remains below 40% and heart rate above 70 bpm despite maximum dose of ACE-I/ARB and BB [37]. Furthermore these patients may also benefit from treatment with Sacubitril/Valsartan, the first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that in last decade has become part of standard therapy for adult HF and it has shown excellent preliminary results in pediatric patients in the ongoing PANORAMA-HF trial (DMD patients included).

In end-stage CMD signs and symptoms of systemic or pulmonary congestion may be clinically evident and loop diuretics are indicated. For chronic use furosemide 1 to 6 mg/kg/die is generally effective, but in some cases the addiction of Metolazone, a thiazide-like diuretic, is required. It is important to underline that there is no evidence of the effectiveness of loop diuretics in improving survival, so they are to be considered only for relieving symptoms [38].

In patients with severe LV dysfunction an antithrombotic therapy should be considered in the primary prevention of thromboembolic events, although not routinely recommended [39].

As mentioned above, DMD patients are at risk of arrhythmias such as atrial fibrillation, atrial flutter and ventricular tachycardia and this risk increases as cardiomyopathy progresses. To date, the management of arrhythmias, with drugs and devices, in DMD-DCM is based on general international guidelines, as there are no specific recommendations for DMD. Implantable cardioverter defibrillator (ICD) has gained acceptance in selected patients [40]. The effectiveness of cardiac resynchronization therapy (CRT) in these patients seems to be poor probably due to the presence of the extensive postero-lateral fibrosis and poorly explored.

Patients with DMD are generally not considered suitable for cardiac transplant candidacy due to early walking impairment, predisposition to respiratory complications, and their short life expectancy. Heart transplant (HTx) has been considered in few highly selected cases in which respiratory compromise was not relevant and reported [40]. In BMD, HTx is considered in end stage phase of CMP.

Few cases of patients with end-stage DMD-DCM and preserved or only mild reduced respiratory function, left ventricle assist device (LVAD) has been considered as a destination therapy [41, 42]. To date, the international literature about LVAD in DMD patients is poor and proper selection of patient and ethical aspect should be accurately evaluated case by case. Share decision making process is also crucial and exploratory dialog with patients and caregivers should be routinely carried out during follow up, not only in urgent situation [43].

Recently, a retrospective study on DMD patients evaluated the effects of advanced cardiac therapies (i.e. ICD, LVAD, HTx) on large DMD population. Out of 436 DMD patients, 9 had ICD placed, 4 had LVAD and 1 HTx. The authors concluded that advanced HF therapies may be used effectively in select subjects with DMD but further studies are needed to stratify the risk and select patients [40].

In the process of choosing about advanced cardiac therapies for end-stage DMD-DCM an in-depth personalized assessment is crucial, and involves the collaboration of the patient and his family with a team of experts composed of cardiologists, cardiac surgeons, neuromuscular specialists, anesthetists, pneumologists, bioethics experts and psychologists.

6. DMD-specific drugs: corticosteroids and new target therapies

Given their effectiveness in slowing the progression of muscle damage and in prolonging the ability to walk and the life-expectancy, corticosteroids such as prednisone and deflazacort have become the standard basic treatment of patients with DMD from the moment of diagnosis or, in any case, by the age of five [44]. While some preclinical studies have suggested that corticosteroids can accelerate cardiomyopathy, subsequent clinical studies have supported their beneficial role in preserving ventricular function and delaying the progression of heart disease, especially by slowing down the inflammation and the fibrotic process and by increasing myogenic repair and myoblast proliferation [45].

Schram et al. [46] showed that steroid therapy was associated with a significantly lower all-cause mortality rate, due to a substantial reduction in HF–related deaths. In this observational study, patients treated with combination of steroid and ACE-I, experienced a much lower incidence of new-onset cardiomyopathy than those treated without steroid.

In recent years a new MRA, called Vamorolone, has been discovered. This new MRA is able to mimic the anti-inflammatory effects of glucocorticoids and it could represent, in the near future, an alternative to the others. It has been reported it seems to have less side effects and greater antifibrotic effect thanks to the inhibition of the aldosterone pathway [47].

Moreover, several other new therapeutic strategies are under investigation, focused to mitigate inflammation and fibrosis or to restore the dystrophin expression. These last strategy includes:

- *the read-through therapies*, such as Ataluren (Translarna™, PTC Therap), the first molecule approved in Europe for DMD, that enables the transcription of mRNA containing premature stop codons;

- *the antisense oligonucleotides (AONs)* that can bind pre-mRNA in specific splicing sites allowing to skip the exons containing mutations and restoring the reading frame of the dystrophin;

- *the viral gene therapies,* that exploit viral vectors to transfer truncated versions of dystrophin gene into myocytes;

- *the upregulation of Utrophin*, a protein similar to dystrophin, that can supply its structural function;

- *the cell based therapies* that consist on the administration of healthy myocytes precursors that can colonize skeletal and cardiac muscle of the recipient.

Most of these gene-targeted therapies are still under study and the evaluation of their efficacy is mainly based on the increased expression of dystrophin in skeletal myocytes and on the slowing of the myopathy progression. Whether these therapies are able to increase dystrophin expression equally in skeletal muscle cells and in cardiomyocytes is still unclear since the heart cannot be routinely biopsied. This is a crucial point as isolated improvement in muscle function would lead to increased demand on a weak heart, accelerating the progression of cardiomyopathy. In particular, Ataluren has shown a modest increase in dystrophin expression in mouse heart, while in a small cohort of humans neither measurable improvement nor deterioration in heart function were observed during 24 months of treatment. Instead, there are strong evidences regarding the benefit on heart function from

gene therapies that use micro-dystrophin genes. In preclinical studies a robust expression of micro-dystrophin in cardiomyocytes has been proved, but the high dose required may be burdened significant side effects and the presence of micro-dystrophin instead of wild-type dystrophin can still lead to the development of a BMD-like cardiomyopathy. Further studies are needed to better understand the long-term effects of these therapies on the heart [48].

6.1 Cardiomyopathy in DMD female carriers

Most women carrying the DMD mutation in one of the two X chromosomes are asymptomatic for life due to the presence of sufficient normal dystrophin produced by the unchanged allele of the gene. Some of these women, called "manifesting carriers", may have mild or moderate forms of myopathy and cardiomyopathy; this is probably due to a mosaic inactivation of the healthy allele in skeletal and heart muscles, or simply to the reduced total amount of normal dystrophin in the cells. In particular, cardiomyopathy can occur in up to 8% of cases and symptoms can appear from adolescence to late adulthood even without any correlation with musculoskeletal manifestations [49]. Therefore, current guidelines recommend to perform echocardiography every 5 years in all adult dystrophinopathy carriers [14]. The severity of disease can vary widely and can worsen during concomitant events such as pregnancy and childbirth. It is interesting to note that in 45% of DMD carriers, subepicardial LGE in the inferolateral free LV wall is detectable at CMR as well as in the initial forms of cardiomyopathy in DMD male patients and this is associated with myocardial enzyme release and with a greater probability of progression of the cardiomyopathy [50].

7. Conclusion

Given the primary role of cardiomyopathy in determining the prognosis of DMD patients, every effort should be focused on preventing or slowing the progression of their cardiac dysfunction. Many drugs commonly used for HF have proven to be quite effective, especially if used from the very early stages of the disease, before heart dysfunction becomes evident. So current recommendations underline the importance of routinely cardiac evaluation since the diagnosis of DMD to early recognize heart abnormalities and start ACE-I. In this preclinical stage of DMD-DCM, CMR plays a substantial role due to its sensitivity in identifying initial areas of fibrotic replacement of the heart muscle. Because of the lack of specific DMD-DCM therapies, current drugs used for HF might be used and further studies are required to address their efficacy, especially at end-stage DCM. To date some new target therapies are available and many others are under evaluation, so that in the near future we will be able to count on a much wider range of specific therapeutic possibilities than now. Moreover, in the end-of- life management, ethical issues are still a matter of intense debate in order to identify potential advanced cardiac therapies candidates. Surely, in this challenging course of treatment, sharing decisions with the patient and his caregivers and the support of a multidisciplinary team are crucial cornerstones for obtaining the best possible results.

Conflict of interest

The authors declare no conflict of interest.

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