Duchenne Muscular Dystrophy: Current Strategies, and What's On the Horizon

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Improvements in neuromuscular and pulmonary clinical management have increased the long-term survival of patients with Duchenne Muscular Dystrophy. With up to 50% of patients in some reports dying from cardiac related complications, cardiomyopathy has emerged as the leading cause of morbidity and mortality in this population [1-3]. This emphasizes the role that cardiac management plays in the overall care in this patient population. By early identification of myocardial changes, and initiation of medical therapy, cardiac specialists may delay the onset and slow the progression of cardiac related disease [1-2]. Here we summarize consensus guidelines that provide guidance for (1) the timing and testing of cardiac surveillance, and (2) current treatment strategies, including the management of advanced heart failure. Finally, we will discuss several revolutionary therapies that hold great promise for improving quality of life, and potentially as stepping-stones toward an eventual cure for DMD.

Surveillance

Early identification of cardiac disease, close monitoring of disease progression and initiation of medical therapy can positively influence the outcome of patients with DMD. Cardiac assessment should begin at the time of DMD diagnosis [1,3]. Evaluation includes a history of past and present disease, family history, clinical examination, EKG and non-invasive imaging [1,3]. Echocardiography is the primary modality used to detect and monitor LV dysfunction [3]. However, images can be limited by poor acoustic windows due to body habitus or the presence of scoliosis [1-3]. In this respect, cardiac MRI is a superior non-invasive imaging modality, more accurate than the echocardiogram for assessing for LV dysfunction and should be considered in patients whenever feasible to perform without anesthesia [1-2]. Birnkrant et. al, also report that cMRI can detect adverse cardiac remodeling before changes are seen in LV function. The extent of myocardial fibrosis is an independent predictor for cardiac arrhythmias, death, or need for transplant. However, cMRI may not be easily accessible due to cost, availability, or the patient's ability to tolerate the procedure. Regular cardiac follow-up is recommended, although guidelines for exact cadence of surveillance is variable. In 2017 the American Heart Association published recommendations for cardiac re-evaluation every 2 years until age 10, then at least annually [3]. The 2018 Care Duchenne Guidelines recommended closer follow-up, annually after diagnosis, because of the recognition that adverse myocardial changes occur before cardiac dysfunction [2].

Current Treatment Strategies

Guideline directed medical therapies for heart failure are commonly used in the care of patients with DMD. In the early stages of the disease, the goal of medical therapy is to delay the onset or progression of heart failure. Early initiation of medications may improve long-terms outcomes [2]. The consensus guidelines clearly define the use of GDMT in patients with HFrEF or with the presence of myocardial changes like LGE on cardiac MRI. In contrast, the use of medications in the absence of dysfunction is varied. ACE inhibition is currently considered the first line therapy for patients with DMD. Available data suggests that prophylactic initiation in patients with normal LV function may delay the progression of heart failure and is associated with higher survival and lower rates of heart failure hospitalizations [4]. The ACTION DMD Therapy Harmonization Protocol recommends that ACE inhibition may be considered pre-emptively at 10 years of age [4]. The DMD Care Considerations describes that the combination of an ACE inhibitor and a mineralocorticoid receptor antagonist slows the decline in LV function after 2 years. Similarly, the AHA guidelines and the ACTION DMD Therapy Harmonization Protocol propose starting MRA therapy when there is evidence of LGE on CMRI, when the LVEF is reduced, or at age 12 if CMRI is not available. DMD Care Considerations and AHA guidelines both recommend beta blockade for DMD patients with reduced systolic dysfunction [1, 3]. It is also reasonable to consider beta blocker in a patient with continued LV dysfunction or elevated heart rates, although it remains uncertain whether sympathetic blunting will affect long-term cardiac outcome [2]. Typically, in patients with severe heart failure, an angiotensin receptor/neprilysin inhibitor has been shown improve heart function. The use of sacubitril/valsartan in patients with DMD has not been studied although extrapolating data from the non-DMD population suggests that patients may benefit [1].

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The management of the DMD patient in severe heart failure include guidance for AICD placement, ventricular assist device, heart transplant, and palliative care. Patients with DMD are at risk for arrhythmia including ventricular tachycardia and atrial fibrillation. Specific benefit for AICD placement as primary prevention in this particular group has not been established, but AICD implantation in patients with LVEF <35% is reasonable on the basis of current adult heart failure guidelines [1]. Heart transplantation is not typically considered a treatment option in this population due to the underlying degenerative and progressive nature of the disease. However, in patients whom maximal medical management has failed (and for whom a heart transplant is not an option), left ventricular assist device may be considered as destination therapy. Destination therapy with LVAD support in this population has been performed more frequently in adult than in pediatric patients, and numerous additional factors must be addressed. A deep understanding of risks and benefits of LVAD support, as well as complex discussions with regards to potential complications, quality of life, psychosocial support, and end of life issues should be held before moving forward [1-2].

New & Emerging Therapies

In recent years, several revolutionary dystrophin restoration strategies have been reported [5-7]. Of these targeted therapies, exon skipping agents are currently most prominent. These agents work by targeting specific regions of the dystrophin gene, excising the problematic exon segment, and linking the two remaining functional ends together [6]. This process results in a truncated version of the dystrophin gene that is less functional than normal type, but still useable. Importantly, exon skipping is not a cure for DMD, but rather partial restoration with production of a truncated dystrophin protein. Further, not all DMD-causing mutations are treatable with exon skipping approaches – current exon skipping therapies have the potential to help an estimated 30-60% of patients [6]. Most clinical trials have focused on problematic "hot-spots," which are between DMD exons 45-55. Since 2016, the FDA has approved 4 exon skipping therapies which are administered via weekly intravenous infusions. These are casimersen (Amondys 45), eteplirsen (Exondys 51), golodirsen (Vyvondys 53), vitolarsen (Viltepso). All have been generally well-tolerated with side effects typically including headaches, flu-like and inflammatory symptoms [6].

Ongoing clinical trials exploring gene replacement therapy using a non-pathogenic viral vector such as adeno-associated virus (AAV) have shown tremendous promise, with early results demonstrating durable clinical improvements in creatine kinase levels and ambulatory assessments [5]. This strategy been shown to prevent progression of cardiac pathology in animal models [8]. Interestingly, AAV is the vector of choice due to its strong skeletal and cardiac muscle tropism, but only has a maximum capacity of 4.8 kb and so cannot deliver the full-length DMD cDNA (~11.5 kb). Thus, micro-dystrophin transgenes (lacking non-essential internal domains) have been developed. Currently 5 different combinations of micro-dystrophin and AAV serotypes are in clinical trials [7]. There have been several treatment-related serious adverse events reported, including myocarditis, muscle weakness, acute kidney injury, transaminitis, and other immune reactions. Additionally, several deaths have also been reported in recipients of high-dose AAV therapy, raising major safety concerns. Aside from safety issues associated with high-dose AAV, as many as 40% of humans are already positive for anti-AAV antibodies because of natural exposure, meaning that they are effectively immunized against the vector itself. Immune reactivity is a key challenge for application of AAV-derived vectors in patients with DMD and pairing with concomitant immunomodulatory strategies is an active area of exploration.

Gene editing with CRISPR/Cas9-mediated techniques have been widely studied in DMD animal models. This remains an area of active research, with numerous trials ongoing in preclinical phase. Multiple CRISPR/Cas9-based strategies have been proposed for treatment of DMD, but low efficiency remains a key challenge for genome editing. Most CRISPR/Cas9 therapies for DMD require AAV vectors for delivery of the gene editing apparatus and are thus subject to the limitations of these delivery vectors.

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Cell therapy using allogenic cardiosphere-derived cell (CDC) has been developed to treat various conditions including cardiomyopathy related to DMD and is undergoing clinical trials evaluating safety and efficacy. The Halt Cardiomyopathy Progression (HOPE) clinical trials are evaluating CAP-1002, which is a CDC consisting of progenitor or precursor healthy donor heart cells. CAP-1002 secretes extracellular vesicles known as exosomes that can modulate the immune system, possess antifibrotic properties and stimulate cellular regeneration. Unique to the study are endpoints specifically evaluating cardiac outcomes in addition to the progression of skeletal muscle myopathy. Phase II of the trial showed improvement in cardiac function and structure and slowed deterioration of upper limb function, and the phase III study (HOPE-3) is in active recruitment [9].

The illness trajectory of the Duchenne muscular disease is well documented with cardiomyopathy as one of the leading causes of morbidity and mortality. Close surveillance and prompt initiation of GDMT are initial steps in slowing the onset and progression of heart disease. The landscape for clinical research of DMD therapy has shifted dramatically in the past few years, with much scrutiny now on various strategies to restore Dystrophin. These emerging therapies, though still hampered with each their own challenges, bring hope for an eventual cure in the not-so-distant future. It remains to be seen whether (and if so, how much) the myocardium will benefit from Dystrophin restoration strategies. Undoubtedly, even extension of skeletal muscle strength alone will expand therapeutic options for DMD patients with end-stage cardiomyopathy, making them more likely candidates for therapies that are not routinely considered at the present time. Expanded treatment options can potentially ameliorate the impact of cardiomyopathy and offer the possibility for increased longevity and improved quality of life.

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