

Duchenne Muscular Dystrophy Cardiac Recommendations for the FDA

As you are aware, muscular dystrophy (MD) is a group of genetically heterogeneous muscle diseases marked by progressive weakness of the skeletal muscles and for some diagnoses, includes a risk of cardiomyopathy (1,2). Duchenne and Becker muscular dystrophy (DBMD) are common forms of muscular dystrophy, with Duchenne muscular dystrophy (DMD) being the most common. DBMD is caused by mutations in the gene that produces the cell membrane protein dystrophin. Deficiency or complete absence of dystrophin causes plasma membrane leakage and muscle fiber and cardiomyocyte degeneration, which leads to progressive muscle weakness, loss of ambulation, respiratory muscle compromise, systolic and diastolic dysfunction, congestive heart failure and arrhythmias (3).

The average age at diagnosis of DMD is approximately five years; delays in motor milestones (such as sitting, standing independently, climbing, and walking) occur much earlier (4). Children with DMD lose their ability to walk independently and become reliant on wheelchairs for ambulation between the ages of 7 and 13 years. For BMD, full time wheel chair use is later. Most individuals with DMD experience serious respiratory, orthopedic, and cardiac complications. By the age of 18, the majority of patients require ventilatory support at night (5, 6). The average life expectancy has significantly increased, however respiratory complications and cardiomyopathy are common causes of death (5). Cardiac disease in DBMD manifests as dilated cardiomyopathy (7, 8) with histologic changes that include alternating areas of myocyte hypertrophy, atrophy and fibrosis (8,9).

Current recommendations for cardiac monitoring and surveillance in DMD were made by the Care Considerations Working Group, which published the Centers for Disease Control and Prevention Care Considerations. These recommendations were made available in 2009 and published in 2010 (4,5). The cardiac recommendations at the time of publication include at a minimum baseline evaluation of cardiac function at diagnosis or before the age of six years, repeat evaluation at least every two years until age 10, with annual evaluations after the age of ten or with the identification of abnormal function and/or the onset of cardiac signs and symptoms. Minimal recommendations for evaluation include an electrocardiogram and non-invasive imaging (such as transthoracic echocardiogram (TTE)). At the time of this publication, cardiac MRI was an emerging imaging modality.

Cardiac evaluation and treatment in the DBMD population improves quality and quantity of life, but is complicated by concurrent skeletal muscle, especially respiratory muscle compromise. Cardiac dysfunction in DBMD does not linearly correlate with musculoskeletal weakness and current genotype/phenotype correlations are limited by outdated cardiac monitoring. Under current guidelines, and in the absence of cardiac symptoms, early manifestations of cardiomyopathy are often under evaluated, unrecognized, and often under treated (10). Although echocardiography is a mainstay of cardiac monitoring, TTE is challenging in the DBMD population. Standard TTE may not detect abnormalities in cardiac function until the second decade of life (11), when EKG and MRI show abnormalities much earlier. Body habitus (obesity with chest wall fibrosis and adiposity, scoliosis, and presence of contractures) contributes to the difficulty of imaging (12). As in most cardiac conditions, evaluation of the right ventricle is difficult using standard TTE. Given concomitant respiratory compromise, evaluation of the right ventricle is relevant. Cardiac MRI with late gadolinium enhancement (LGE) has been

found to be a sensitive, objective, reproducible, non-invasive method of monitoring cardiac tissue structure and function, providing high-resolution images produced without the use of ionizing radiation (13). MRI is less affected by body habitus and has demonstrated early cardiac involvement in the presence of a normal evaluation by TTE (14,15). Early detection of cardiomyopathy in this population is essential for the initiation of cardioprotective medical therapies, which may slow cardiac remodeling and reduce the progression of cardiomyopathy to symptomatic heart failure (11,16-19). The sensitivity and reproducibility of MRI to detect early abnormal findings or subtle longitudinal changes, such as the detection of ventricular dysfunction or the presence of fibrosis, offers significant value to the management of cardiomyopathy in Duchenne (20). LGE, in particular, offers considerable diagnostic and prognostic value across a broad spectrum of nonischemic myocardial diseases (21), including DBMD (22). Advanced echocardiography techniques, such as tissue Doppler and strain measurements, may also be useful to detect early cardiac changes, but these are not routinely incorporated into clinical exams or clinical trials.

The use of imaging is not novel in therapeutic drug development. Imaging has long been used in the early phases of clinical trials (Phases I and II), and more recently has been used to provide primary or secondary endpoints for phase III trials. Draft guidance around imaging has been provided to industry by the Food and Drug Administration (FDA) (23, 24, 25, 26). This draft guidance states that imaging is acceptable for the identification and monitoring of structure delineation, disease or pathology detection or assessment; functional, physiological or biochemical assessment; and diagnostic or therapeutic patient management. This draft guidance has also states that aspects of imaging (imaging outcomes, primary efficacy endpoints and statistical analysis of the primary endpoint) must be standardized when imaging outcomes define an objective primary endpoint in a phase 3 trial or when important quantitative outcome data is acquired via imaging. Primary efficacy endpoints must be objective and include functional, physiologic and pathological measures and/or image characteristics) and may need to include measures of clinical usefulness if the value of the imaging information is not clear. These standardized measures and techniques exceed those recommended for medical care, and includes standardized processes of image acquisition, interpretation and data archiving.

It is our opinion that clinical trials of muscle therapies for patients with DMD, especially those testing therapies in younger DMD patients, often have inadequate cardiac monitoring and rarely have cardiac endpoints. In light of these findings, the NHLBI Contemporary Cardiac Issues in Duchenne Muscular Dystrophy working group convened July 10-11, 2014 and recommended the following protocol for cardiac surveillance in current and future clinical trials:

All Phase II or III trials of muscle therapies have sufficient cardiac monitoring with cardiac MRI.

Cardiac MRI with LGE should be considered standard of care in every phase 2 or 3 clinical trial, and in phase 1 clinical trials lasting more than 6 months and evaluating therapeutic endpoints

Any protocol excluding cardiac monitoring should have sound rationale and protocol review by appropriate cardiac expertise to review justification.

Consideration should also be given to incorporating additional cardiac endpoints into the trial design when appropriate.

Cardiac MRI with LGE is standard of care; however transthoracic echocardiogram is acceptable if:

- Participant would require sedation for the cardiac MRI
- Participants are under age 6 years

MRI protocol should include:

- Cine imaging in standard long-axis and contiguous short-axis planes (real-time cine is an excellent alternative for subjects who have difficulty breatholding)
- Evaluation of late gadolinium enhancement indicating the presence of myocardial injury, unless contraindicated.
- Strong consideration should be given to including tagging as this may provide better measurements of early cardiac involvement

Duchenne cardiomyopathy and heart failure directly impacts survival. Accordingly, any therapeutic trial should consider the implications of the specific therapy on the cardiovascular disease associated with DMD.

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