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Use of advanced heart failure therapies in Duchenne muscular dystrophy

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ABSTRACT

Background: As survival and neuromuscular function in Duchenne Muscular Dystrophy (DMD) improve with glucocorticoid therapy and respiratory advances, the proportion of cardiac deaths is increasing. Little is known about the use and outcomes of advanced heart failure (HF) therapies in this population.

Methods: A retrospective cohort study of 436 males with DMD was performed, from January 1, 2005-January 1, 2018, with the primary outcome being use of advanced HF therapies including: implantable cardioverter defibrillator (ICD), left ventricular assist device (LVAD), and heart transplantation (HTX).

Results: Nine subjects had an ICD placed, 2 of whom (22.2%) had appropriate shocks for ventricular tachycardia; 1 and 968 days after implant, and all of whom were alive at last follow-up; median 18 (IQR: 12.5–25.5) months from implant. Four subjects had a LVAD implanted with post-LVAD survival of 75% at 1 year; 2 remaining on support and 1 undergoing HTX. One subject was bridged to HTX with ICD and LVAD and was alive at last follow-up, 53 months after HTX.

Conclusion: Advanced HF therapies may be used effectively in select subjects with DMD. Further studies are needed to better understand risk stratification for ICD use and optimal candidacy for LVAD implantation and HTX, with hopes of improving cardiac outcomes.

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common form of the childhood muscular dystrophies, with prevalence estimates of 1.02/10,000 males in the Unites States and 4.78/100,000 males worldwide [1,2]. Untreated, DMD has a predictable clinical course marked by progressive skeletal muscle weakness with loss of ambulation typically by age 12 and death occurring in early adulthood secondary to respiratory or cardiac failure. Cardiac disease in DMD manifests as dilated cardiomyopathy (CM) and/or cardiac arrhythmia and the incidence of DMD CM has been shown to increase with age [3,4]. Although it is estimated that 25% of boys with DMD have CM by 6 years of age,

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cardiac involvement is nearly ubiquitous in older patients, as > 90% of men > 18 years of age demonstrate evidence of cardiac dysfunction [5]. Survival, neuromuscular function, and quality of life in DMD are improving due to treatment with glucocorticoids and advances in respiratory care and therefore, cardiac disease is increasing as a major cause of death. Kieny et al., recently analyzed a cohort of adult DMD patients and found that cardiac causes of death increased from 8% to 44% over a 30 year period (1981–2011) [6–8].

In recent years, there have been significant advances in the management of DMD CM including the expanded use of cardiac MRI for surveillance of myocardial damage and function, expanded consideration of existing heart failure (HF) pharmacologic therapies, and the exploratory use of advanced non-pharmacologic HF therapies, including implantable cardioverter-defibrillator (ICD), mechanical circulatory support (more specifically, left ventricular assist device (LVAD)), and heart transplantation (HTX) [9]. It remains unclear how best to use advanced HF therapies to optimize clinical outcomes in DMD CM as data are lacking. There is no published data on the use of ICD specifically for DMD CM and there has been concern that the risk of intervention may be greater for this population [9]. Data on the use of LVAD for DMD have been limited to case reports and case series, the largest of which is an Italian series of 7 patients (6 of whom have DMD) with median follow-up of 21.7 months (range 3–45), in which all patients survived to hospital discharge with 3 deaths in the medium term (range 14–54 months) post-implant. This led the authors to conclude that the use of an LVAD as destination therapy in patients with DMD CM is feasible and may be suitable as palliative therapy [10–12]. Finally, there is some data on clinical outcomes after HTX in muscular dystrophy patients showing outcomes to be similar to those seen in age-matched patients with non-ischemic cardiomyopathy. However, only 3/27 patients analyzed in a retrospective review of the Cardiac Transplant Research Database were diagnosed with DMD [13]. Given the limited data on the use of advanced HF therapies for DMD CM we sought to analyze a large cohort of patients followed across North America to evaluate the outcomes of those in whom advanced HF therapies (ICD, LVAD, and HTX) were used and we believe this to be the first study of its kind.

2. Methods

A retrospective cohort study was conducted at 17 pediatric hospitals (Supplemental Table 1) across North America (16 United States, 1 Canada) analyzing cases with DMD from which clinical information acquired between January 1, 2005 and December 31, 2015 was collected by each site investigator. For those cases in which advanced HF therapies were used (ICD, LVAD, HTX) follow-up was extended through January 1, 2018. Inclusion criteria included males with the diagnosis of DMD who had ≥ 2 cardiac evaluations (defined as 2 echocardiograms (ECHO) at least 11 months apart) at their home institution. The diagnosis of DMD was determined by clinical record review; though genetic testing data was collected, this was not mandatory for inclusion. Exclusion criteria included females and the diagnosis of congenital heart disease. The clinical approach used to determine candidacy for advanced therapies was site specific. Data points collected included but were not limited to: age of diagnosis, age ambulation ceased, respiratory support needed, use of steroids, all cardiac testing (including ECHO, electrocardiogram, cardiac MRI, and Holter monitor), cardiac medication use, implantation of ICD, implantation of VAD, HTX, date of death, and cause of death. Cardiac testing data was acquired from study reports and not interpreted independently for this study. Severe LV systolic dysfunction was defined as an ejection fraction (EF) < 30% or fractional shortening (FS) < 16% by ECHO. Each investigator obtained IRB approval at their own institution and Data Use Agreements were established on an as needed basis. Study data were collected and managed using an electronic database hosted at the University of Rochester Medical Center.

Table 1
Selected characteristics of Duchenne muscular dystrophy cases.

Selected characteristics (N = 436)	
Median age of Duchenne muscular dystrophy diagnosis	4 (IQR: 3–6) years
Median age of those alive at study end	14.9 (IQR: 11–19.1) years
Median age ambulation ceased	11 (IQR: 9–12) years
Number ambulating at study start	133 (31%)
Median fractional shortening at study start (N = 401)	33 (IQR: 29–36)%*
Median fractional shortening at study end (N = 381)	31 (IQR: 25–34)%*
During study period	N = (%)
Treated with glucocorticoids	333 (77%)
Treated with cardiac medications	
Angiotensin converting enzyme inhibitor	246 (56%)
Beta-blocker	111 (25%)
Aldosterone antagonist	39 (9%)
Digoxin	28 (6%)
Tracheostomy placement	24 (6%)
Death prior to study end	N = 29 (6.7%)
Median Age at death (N = 28)	19 (IQR:15–31) years

* $p < 0.001$.

2.1. Statistical analysis

Statistical analyses were conducted using Stata 13.1 (StataCorp LP, College Station, TX). All variables were assessed for normality prior to analysis and expressed as mean ± standard deviation for parametric and median (interquartile range (IQR)) for non-parametric distributions. Group differences were tested using Student's t-test or Wilcoxon rank-sum, as appropriate; proportions by a chi-squared test. Significance was defined using a two-tailed hypothesis test with $p < 0.05$.

3. Results

Four hundred and thirty-six males with DMD were studied; median age of DMD diagnosis was 4 (IQR: 3–6) years and median age at study end was 14.9 (IQR: 11–19.1) years. At the start of the study period, 31% were ambulatory and 77% had been treated with glucocorticoids. Selected characteristics of subjects are outlined in Table 1. At the end of the study period 29 subjects were deceased (6.8%) and 18 (4.2%) were lost to follow-up. Forty-three (4.9%) subjects had severe LV systolic dysfunction during the study period, and of these with known status at study-end, 12/41 (29.3%) died, at a median of 2.1 (IQR 1.1–4.4) years from the time severe LV systolic dysfunction was diagnosed, compared to 17/367 (4.6%) without severe LV systolic dysfunction ($p < 0.001$). Selected characteristics of subjects with severe LV systolic dysfunction are outlined in Table 2. For the overall cohort, median age at death was 19 (IQR: 15–31) years with the most common cause of death being respiratory in nature (n = 8, 27.6%) followed by sudden cardiac death (SCD, n = 6, 20.7%). Other causes of death included multi-organ failure (n = 3), progressive heart failure (n = 3), stroke (n = 1), and unknown/other (n = 8).

3.1. Implantable cardioverter-defibrillator

Nine (2.1%) subjects had an ICD placed at a median age of 19 (IQR: 17–33) years. Indication for ICD placement was non-sustained ventricular tachycardia (NSVT), n = 6 (67%) and poor ventricular function, n = 3 (33%). FS prior to ICD placement based on indication for ICD placement was 17.4% for NSVT (moderately decreased, n = 5) and 9% (severely decreased, n = 3), p = 0.1. Two (22.2%) subjects, both of whom had the ICD placed for NSVT, had appropriate shocks for VT; 1 and 968 days after implant. No subject had an inappropriate shock or lead infection. One subject had a lead fracture. All subjects with an ICD were alive at last follow-up; 8 with device still in place at a median of

Table 2
Selected characteristics of Duchenne muscular dystrophy cases with severe Left Ventricular Systolic Dysfunction ($N = 43$).

	Died during study period ($N = 12$)[a]	Alive at study end ($N = 29$)[a]	p value
Median age at death/study end	20.8 (IQR 15-9-24.6) years	19.6 (IQR 17.0–22.1) years	0.61
Median age ambulation ceased[b]	9 (IQR 9–12) years	11 (IQR 10–13) years	0.15
Current/past steroid use	6 (50%)	22 (75.9%)	0.11
Heart failure admission	5 (41.7%)	7 (24.1%)	0.26
VAD implanted	1 (8.3%)	2 (6.9%)	0.87
ICD implanted	0 (0%)	9 (31%)	0.03
Medication use at last cardiac evaluation[c]			
Ace-inhibitor/angiotensin Receptor Blocker	10/11 (90.9%)	28/31 (90.3%)	0.96
Beta-Blocker	7/11(63.6%)	20/31 (64.5%)	0.96
Ace-inhibitor/Angiotensin Receptor Blocker + Beta-Blocker	6/11 (54.5%)	18/31 (58.1%)	0.84

[a] Lost to follow-up: $N = 2$.
[b] Data available for $N = 35$.
[c] Missing data for 1 deceased subject.

24 (IQR: 19–32) months from implant. One subject had the ICD removed at time of HTX (13 months after implant). A greater percentage of subjects with severe LV systolic dysfunction who were alive at study end had an ICD implanted compared to those with severe LV systolic dysfunction who died during the study period ($p = 0.03$, see Table 2).

3.2. Left ventricular assist device

Four subjects (0.9%) had a LVAD implanted at a median age of 17 (IQR: 16–23) years. The median time from DMD diagnosis to LVAD implant was 10.4 (IQR: 5.5–13.3) years. EF prior to implant ranged from 21 to 29% ($n = 3$). Three subjects (75%) were hospitalized prior to implant and all subjects were discharged home on device. LVAD characteristics are summarized in Table 3. Post-LVAD survival was 75% at 1 year, with 2 patients remaining on support and 1 undergoing HTX. There was 1 VAD death at 5 months from an embolic stroke. There was an additional death at 15 months of unknown causes. LVAD complications occurred in 3 subjects (75%); range 5–16 months from implant.

3.3. Heart transplantation

One male subject with DMD received a HTX after being bridged to transplant with both an ICD (13 months) and LVAD (10 months). Age at HTX was 18 years and time from DMD diagnosis to HTX was 6.4 years. For this subject, ambulation ceased at 16 years. Respiratory support at the time of HTX was nightly continuous positive airway pressure (CPAP). Post-HTX hospitalization was 15 days. This subject was alive at study end, 53 months from HTX.

4. Discussion

DMD is the most common form of the childhood muscular dystrophies with cardiac involvement that is nearly universal in older patients. As survival, neuromuscular function, and quality of life in DMD are improving due to treatment with glucocorticoids and advances in respiratory care, cardiac disease is increasing as a major cause of death. Our data shows that a significantly greater proportion of those with severe LV dysfunction died compared to those without. Fortunately, research into various treatment strategies for DMD is rapidly expanding. Given this, it is important for us to understand how best to support patients with advanced cardiac disease, and if non-

Table 3
Left Ventricular Assist Device (LVAD) Characteristics.

Age at implant (years)	Respiratory support at time of implant	Ambulating	Device implanted	Goal of LVAD[a]	Home on device	LVAD[a] complication (months from implant)	Alive as of 1/1/2018 (months from implant)	Cause of death
17	Nightly BIPAP[b]	No	HeartWare	Destination therapy	Yes	Yes, pump thrombosis (16)	Yes, with device (18)	
17	Nightly CPAP[c]	No	HeartMate II	Bridge to transplant	Yes	No	Yes, heart transplant (10)	
29	SIP ventilator	No	HeartMate II	Destination therapy	Yes	Yes, gastrointestinal bleed (10)	No, deceased (15)	Unknown
15	Nightly CPAP[c]	No	HeartWare	Bridge to decision	Yes	Yes, stroke (5)	No, deceased (5)	Stroke with hemorrhagic conversion

[a] Left Ventricular Assist Device.
[b] Bilevel positive airway pressure.
[c] Continuous positive airway pressure.

pharmacologic HF therapies, including ICD, LVAD, and HTX can be used effectively which was the basis for this study.

With regards to the use of ICD for SCD prevention, 22% of subjects with an ICD had an appropriate shock and all were alive at last-follow-up. Importantly, only 1 subject experienced a complication and the rate of complications does not appear higher when compared to other pediatric populations. Maron et al. analyzed a large pediatric cohort of high-risk subjects with hypertrophic cardiomyopathy and found a significant rate of ICD complications, particularly inappropriate shocks and lead malfunction, which occurred in 41% of their cohort [14]. Admittedly, our sample size is small and there remains a need for more studies on this topic as screening and therapy for cardiac arrhythmias in DMD are understudied areas and the natural history of rhythm abnormalities in this disease has not been well documented in the literature. More specifically, as we have shown that SCD is a major cause of death in DMD and further that a greater percentage of subjects with severe LV systolic dysfunction who were alive at study end had an ICD implanted compared to those with severe LV systolic dysfunction who died during the study period, the use of ICD for SCD prevention warrants further analysis.

LVADs were implanted in a small percentage of our cohort most often as destination therapy (2/4, 50%), with all patients being discharged home alive post-implant. Post-LVAD survival was 75% at 1 year, with two subjects remaining on support and 1 undergoing HTX. There was an additional death at 15 months of unknown causes with the remaining subject still alive on LVAD support at study end. Three subjects (75%) experienced a LVAD complication during the study period which is significant. However, a high rate of complications has been reported in larger series on VAD use in children; the 2nd annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) report described an overall actuarial survival of all pediatric VAD subjects at 6 months of 72% with at least one major adverse event occurring in 58% of subjects [15]. Similarly, HTX was used infrequently, with only 1 subject receiving a HTX after being bridged to transplant with both an ICD and LVAD. This subject was discharged home alive shortly after transplant, was alive at study end, and was transitioning to an adult transplant program. Importantly, candidate selection for LVAD implementation and HTX remains complex and neuromuscular challenges must be factored in. The importance of larger registries that collect data on LVAD use is highlighted as more collective experience with regard to LVAD use for DMD CM is needed. Nevertheless, we believe that our data supports the consideration of LVAD use and HTX for advanced HF management in carefully selected patients with DMD.

This study is limited with regards to small sample size for each of the advanced HF therapies, thereby prohibiting more advanced statistical analysis. However, we believe this to be the largest multi-center study evaluating the use of advanced HF therapies in DMD to date. Although this is a large, multi-center study, we were not able to collect data from all pediatric centers offering advanced HF therapies and so we likely missed cases in which ICD, LVAD, and HTX were used for DMD patients. Further, we did not collect data in such a way that we could determine if an advanced HF therapy was considered but ultimately the patient was deemed not a candidate. Finally, though the goal of this study was to collect data on all eligible subjects at each site, the means of subject identification was left up to each site investigator and so potential subjects could have been missed.

In conclusion, although rarely utilized, advanced HF therapies may be used effectively for end-stage CM in carefully selected patients with DMD. Further studies are needed to better understand risk stratification for ICD use and prevention of sudden cardiac death as well as optimal candidacy for and timing of LVAD implantation and referral for HTX, with hopes of improving cardiac outcomes in those affected by DMD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ppedcard.2019.01.001.

Declaration of interest

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