[Pulmonary and Cardiovascular Original Research]

CHEST

Cardiorespiratory Progression Over 5 Years and Role of Corticosteroids in Duchenne Muscular Dystrophy

A Single-Site Retrospective Longitudinal Study

Federica Trucco, MD; Joana Domingos, MD†; Chee Geap Tay, MD; Deborah Ridout, MSc; Kate Maresh, MD; Pinki Munot, MD; Anna Sarkozy, PhD; Stephanie Robb, MD; Rosaline Quinlivan, PhD; Mollie Riley, PT; Michael Burch, PhD; Matthew Fenton, PhD; Colin Wallis, PhD; Elaine Chan, MD; Francois Abel, MD; Adnan Manzur, PhD; and Francesco Muntoni, PhD

BACKGROUND: Corticosteroids (CSs) have prolonged survival and respiratory function in boys with Duchenne muscular dystrophy (DMD) when compared with CSs-naïve boys.

RESEARCH QUESTION: The differential impact of frequently used CSs and their regimens on long-term (> 5 years) cardiorespiratory progression in children with DMD is unknown.

STUDY DESIGN AND METHODS: This was a retrospective longitudinal study including children with DMD followed at Dubowitz Neuromuscular Centre, Great Ormond Street Hospital London, England, from May 2000 to June 2017. Patients enrolled in any interventional clinical trials were excluded. We collected patients' anthropometrics and respiratory (FVC, FVC % predicted and absolute FVC, and noninvasive ventilation requirement [NIV]) and cardiac (left ventricular shortening function [LVFS%]) function. CSs-naïve patients had never received CSs. Patients who were treated with CSs took either deflazacort or prednisolone, daily or intermittently (10 days on/10 days off) for > 1 month. Average longitudinal models were fitted for yearly respiratory (FVC % predicted) and cardiac (LVFS%) progression. A time-to-event analysis to FVC % predicted < 50%, NIV start, and cardiomyopathy (LVFS < 28%) was performed in CS-treated (daily and intermittent) vs CS-naïve patients.

RESULTS: There were 270 patients, with a mean age at baseline of 6.2 ± 2.3 years. The median follow-up time was 5.6 ± 3.5 years. At baseline, 263 patients were ambulant. Sixty-six patients were treated with CSs daily, 182 patients underwent CSs intermittent > 60% treatment, and 22 were CS-naïve patients. Yearly FVC % predicted declined similarly from 9 years (5.9% and 6.9% per year, respectively; $P = .27$) in the CSs-daily and CSs-intermittent groups. The CSs-daily group declined from a higher FVC % predicted than the CSs-intermittent group ($P < .05$), and both reached FVC % predicted < 50% and NIV requirement at a similar age, > 2 years later than the CSs-treated group. LVFS% declined by 0.53% per year in the CSs-treated group irrespective of the CSs regimen, significantly slower ($P < .01$) than the CSs-naïve group progressing by 1.17% per year. The age at cardiomyopathy was 16.6 years in the CSs-treated group ($P < .05$) irrespective of regimen and 13.9 years in the CSs-naïve group.

INTERPRETATION: CSs irrespective of the regimen significantly improved respiratory function and delayed NIV requirement and cardiomyopathy. CHEST 2020; ■(■):■-■

KEY WORDS: cardiorespiratory; corticosteroids; Duchenne muscular dystrophy

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

Cardiorespiratory complications have a major impact on survival of patients with Duchenne muscular dystrophy (DMD). Along with anticipatory cardiorespiratory care,[1,2] long-term corticosteroids (CSs)[3] have prolonged patients' survival[4,5] and delayed cardiomyopathy.[6-8] Although the rate of progression of cardiomyopathy in CSs-naïve patients is known, the extent of protection provided by CSs is debated, and the difference of the two regimens is unknown.

The role of steroids on DMD respiratory function is also an unresolved issue. Previous studies have reported a similar respiratory decline in CSs-treated and CSs-naïve patients,[9-11] and in patients treated with different steroid treatments[12]; others have shown that boys with DMD treated with CSs aged 7 to 18 years maintained higher FVC % predicted than age-matched CSs-naïve boys[13,14] and reached FVC < 50% predicted and absolute FVC < 1 L later.[15]

CSs regimens most commonly used are daily and intermittent (most patients 10 days on/10 days off; in the past also 10 days on/20 days off). The intermittent regimen was proposed to limit the severity of chronic CSs-related side effects.

We hypothesized that the two mostly used CSs, deflazacort and prednisolone, administered intermittently or daily, would differentially affect the cardiorespiratory progression (FVC % predicted and left ventricular shortening fraction [LVFS%]) and the age to meaningful cardiorespiratory end point (FVC < 1 L, NIV requirement, and LVFS% < 28%) in a large UK pediatric cohort of DMD. We additionally hypothesized that the cardiorespiratory progression and the age at cardiorespiratory end point would be different in CSs-treated and CSs-naïve patients.

Methods

Study Design

This was a retrospective study of pediatric patients with DMD (< 18 years of age) followed at the Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, England, from May 2000 to June 2017. We included patients whose parents consented to the NorthStar database. UK national Ethics Committee and Institutional Review Board approved the NorthStar UK Network for data collection and the conduct of research studies within the network.

Patients enrolled in any interventional clinical trials were excluded. Patients in the Heart Protection Trial[16,17] were further excluded from the cardiac analyses (e-Fig 1).

Patients Characteristics and Genotyping Information

All information was collected from medical records. The first visit recorded for each patient at the enrollment of the study was defined as baseline. Clinical visits were carried out every 6 months from 5 years of age onward. Lung function was performed at every visit, whereas echocardiogram was performed yearly. Height was assessed standing for ambulant patients, or calculated from arm span in nonambulant patients. Ambulatory status was recorded at each visit. Loss of ambulation (LoA) was the inability to walk independently for 10 m. Scoliosis was defined as a Cobb angle > 20°[1] from spine radiograph. Age at time of scoliosis surgery was collected. None of the patients enrolled were on ventilator support (noninvasive ventilation [NIV]) at baseline until the time to the primary respiratory end point. No patients were on any cardiac medication at the baseline visit. Dystrophin (*DMD*) gene mutations were analyzed by multiplex ligation-dependent probe amplification, polymerase chain reaction, or direct sequencing. We stratified patients based on their lack of dystrophin isoforms. Dp427, produced in skeletal and cardiac muscle, is affected by all mutations. The shorter isoforms are produced by promoters spread along the *DMD* gene. Patients carrying mutations in exons 1 to 79, 30 to 79, 45 to 79, 56 to 79, and 63 to 79, respectively, lack Dp427, Dp260, Dp140, Dp116, and Dp71. Dp116 is expressed in cardiac muscle and peripheral nerve,[18-20] and Dp71 is expressed in lung, skeletal, and cardiac muscle besides the brain and kidney.[21-24] Cardiorespiratory

ABBREVIATIONS: CS = corticosteroid; DMD = Duchenne muscular dystrophy; HR = hazard ratio; IQR = interquartile range; LVFS% = left ventricular fractional shortening; LoA = loss of ambulation; NIV = noninvasive ventilation

AFFILIATIONS: From the Dubowitz Neuromuscular Centre (Drs Trucco, Domingos, Tay, Maresh, Munot, Sarkozy, Robb, Quinlivan, Manzur, and Muntoni), UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital, London, England; the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Care (Dr Trucco), University of Genoa, Genoa, Italy; the Department of Paediatrics (Dr Tay), University of Malaya, Kuala Lumpur, Malaysia; the Population, Policy and Practice Research and Teaching Department (Ms Ridout), UCL GOS Institute of Child Health, London, England; the NIHR Great Ormond Street Hospital Biomedical Research Centre (Ms Ridout and Dr Muntoni), Great Ormond Street Institute of Child Health, University College London, & Great Ormond Street Hospital Trust, London, England; the MRC Centre for Neuromuscular Disease (Dr Quinlivan), National Hospital for Neurology and Neurosurgery, London, England; and the Lung Function Laboratory (Dr Riley), the Department of Cardiology (Drs Burch and Fenton), and the Department of Respiratory Medicine (Drs Wallis, Chan, and Abel), Great Ormond Street Hospital, London, England.

[†]Deceased.

Drs Trucco and Tay contributed equally to this manuscript.

FUNDING/SUPPORT: This study is supported by the Muscular Dystrophy UK to the Neuromuscular Centre at UCL and to the North Star network (www.northstardmd.com). Dr Muntoni is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health, University College London, and Great Ormond Street Hospital Trust, London, England.

CORRESPONDENCE TO: Francesco Muntoni, PhD, Dubowitz Neuromuscular Centre, UCL GOS Institute of Child Health and Great Ormond Street Hospital, London, 30 Guilford St, WC1N 1EH, London, England; e-mail: f.muntoni@ucl.ac.uk

DOI: https://doi.org/10.1016/j.chest.2020.04.043

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

progression was analyzed in patients lacking Dp71 and Dp116[19] and in patients amenable to exon 44, 45, 51, or 53 skipping.[25-27]

CSs Regimens

CSs-naïve patients had never received CSs therapy. CSs-treated patients took either daily or intermittent CSs (10 days on/10 days off) for > 1 month. CSs consisted of prednisolone 0.9 mg/kg or deflazacort 0.75 mg/kg. The CSs dose was collected throughout the study period for all visits. There was a slight difference in the management of CSs throughout the study. CSs dose was adjusted for weight and tapered down when patients reduced their ability to walk up to a minimum dose of prednisolone 0.3 mg/kg and deflazacort 0.4 mg/kg. The boys who had mixed steroids or regimens were defined as switchers. For these patients, we explored two CSs and regimens definitions to compare daily vs intermittent. As per previous work by Ricotti et al,[28] we have defined, for each patient, either patients' treatment at study baseline or the majority CSs regimen they were treated with. We have considered for each patient the total duration of the observation and considered the regimen he/she was treated with for ≥ 60% observation time. Results were similar, and we have presented the most clinically relevant majority treatment, defined as CS-daily and CS-intermittent. Patients' treatment was labeled as deflazacort or prednisolone based on the majority CS. Patients whose CSs information was missing were called not known. They were excluded from the CSs regimens comparison. For patients who stopped CSs during the study, only data prior to stopping were included.

Respiratory Status Outcomes

Spirometry was performed in a seated position according to European Respiratory Society/American Thoracic Society guidelines.[29] Absolute FVC in liters was collected, and FVC % predicted was calculated according to reference data.[30]

We considered age when FVC % predicted < 50% as the main respiratory end point,[1] and age to absolute FVC < 1 L and requirement of NIV as secondary end points. Absolute FVC < 1 L is known to predict nocturnal hypoventilation.[31,32]

The yearly progression of FVC % predicted and FVC and the time to clinically meaningful respiratory end points were compared between CSs regimens and between the CSs-treated and CSs-naïve groups.

Cardiac Status Outcomes

The LVFS% was used for cardiac progression analysis. LVFS% was defined as the change in diameter of the left ventricle between the contracted and relaxed states.[33] LVFS% was used as more easily available and less prone to interscorer variability than the Simpson left ventricular ejection fraction in patients with DMD with a poor echogenic window.[34]

We considered as the onset of cardiomyopathy as the main cardiac end point, defined as LVFS < 28%. This threshold has been previously considered as clinically meaningful in several studies focused on cardiac function in DMD and other muscular dystrophies.[7,34]

The yearly progression of LVFS% and the time to cardiomyopathy were compared between CSs regimens and between CSs-treated and CSs-naïve groups.

We recorded the use and the age at the start of ACE-inhibitors and beta-blockers. They were started by the cardiology team based on patients' cardiac function and clinical symptoms (e-Appendix 1).

Statistical Analysis

Characteristics of the sample are presented as mean ± SD or median (range or interquartile range [IQR]) for skewed data and frequency (%) for categorical data.

For LVFS% and FVC % predicted, we describe the longitudinal trajectories and estimate the mean annual change using mixed effects regression models, accounting for the longitudinal data and age at baseline. Models were fitted including patient as a random effect and CSs regimen (intermittent or daily) and treatment (deflazacort or prednisolone) as fixed effects, using an unstructured correlation matrix. For FVC % predicted, we considered the decline after the age of 9 years onward because respiratory capacity continues to increase until up to this age. We compared rates of decline between CSs regimens in a separate set of models according to patients' amenability to exon 44, 45, 51, and 53 skipping, using appropriate interaction terms. Results are presented as mean annual change, or difference in mean annual change between subgroups, with 95% CIs.

Using Kaplan-Meier analysis, we estimated the median age at which clinically meaningful end point occurred: LoA, scoliosis, NIV, cardiomyopathy (LVFS < 28%), FVC % predicted < 50%, and FVC < 1 L. We used Cox regression analysis to investigate whether the average age at which these events occurred varied according to majority CSs and regimen through the inclusion of an interaction term, and hazards ratios (HRs) with 95% CIs are presented. We compared the estimated age at respiratory and cardiomyopathy end point by Dp71 and Dp116 isoform deficiency. The proportional hazards assumption was checked for all Cox models, by inspection of log-log plots and formal testing of Schoenfeld residuals. We present estimated median time to event only where this assumption was unclear.

All analyses were conducted in Stata v15 (StataCorp) with significance level of $P < .05$.

Results

Study Population

There were a total of 270 patients, with a mean of eight visits per patient. The mean age at the baseline visit was 6.2 ± 2.3 years; the mean follow-up time was 5.6 ± 3.5 years. Seventy-seven boys (29%) transitioned to adult care, and 36 (13%) were lost to follow-up. Seven boys (2%) died (cardiomyopathy: n = 1, after general anesthesia: n = 1, no information: n = 5), with a mean age of 16.5 ± 3.8 years. At the time of death, three patients had stopped CSs and four were still CSs treated (CSs daily: n = 2, CSs intermittent: n = 2) (Table 1).

At the baseline visit, 263 boys (97%) were ambulant, with a mean age of 6.0 ± 2.1 years. Seven patients (3%) were nonambulant, with a mean age of 11.5 ± 2.9 years. At the last assessment, 140 patients (52%) were ambulant. The median age at LoA was 12.1 years (IQR, 4.5) in the whole population, 12.5 years (IQR,5.7) in the CSs-daily group, 12.0 years (IQR, 4)

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

TABLE 1] Clinical and Genetic Features of the Study Population (N = 270) and Cardiac Cohort (n = 229)

Feature	Total Population		Cardiac Cohort[a]	
	No. or No. (%)	Mean Age ± SD (y)	No. or No. (%)	Mean Age ± SD (y)
Age at diagnosis	255	4.5 ± 2.3	216	4.4 ± 2.4
Age at first visit	270	6.2 ± 2.3	229	6.2 ± 2.3
Age at last visit	270	12.1 ± 4.0	229	11.9 ± 4.2
Age at starting CSs	248	6.2 ± 1.7	208	6.3 ± 1.8
CSs regimen (≥ 60% treatment)				
Daily	66 (25)	5.8 ± 1.4	52 (23)	5.8 ± 1.5
Intermittent[b]	182 (67)	6.4 ± 1.8	156 (68)	6.4 ± 1.8
Naïve	22 (8)	…	21 (9)	…
Deflazacort (≥ 60% treatment)	36 (12.3)	…	43 (17.1)	…
Prednisolone (≥ 60% treatment)	204 (69.6)	…	166 (65.9)	…
CSs regimen and compound (n = 240)				
Daily deflazacort	14 (4.8)	…	14 (5.6)	…
Intermittent deflazacort	22 (7.5)	…	29 (11.5)	…
Daily prednisolone	50 (17.1)	…	38 (15.1)	…
Intermittent prednisolone	154 (52.6)	…	127 (50.4)	…
Stopped steroids	38 (13)	…	33 (13)	…
Daily	5	…	2	…
Intermittent	32	…	30	…
Not known	1	…	1	…
Steroid switchers				
Daily to intermittent	0 (0)	…	…	…
Intermittent to daily	39 (12.5)	8.9 ± 2.2	…	…
Amenable to exon skipping				
Exon 44	20 (7.4)	…	16 (7.0)	…
Exon 45	23 (8.5)	…	21 (9.2)	…
Exon 51	29 (10.7)	…	24 (10.5)	…
Exon 53	21 (7.8)	…	20 (8.7)	…
Mutations leading to lack of Dys isoforms				
Dp427	270 (100)	…	229 (100)	…
Dp116	28 (10)	…	27 (18)	…
Dp71	18 (7)	…	18 (8)	…

CS = corticosteroid.
[a]Cardiac cohort: patients in the Heart Protection Trial were excluded from the overall population for cardiac progression analyses.
[b]Intermittent regimen: 10 days on/10 days off CSs.

in the CSs-intermittent group, and 10.5 years (IQR, 2.1) in the CSs-naïve group. The CSs-naïve group lost ambulation at a similar age of the CSs-daily (P = .09) and CSs-intermittent (P = .34) groups. Fifty-seven patients (21%) had scoliosis. Five had scoliosis already at baseline, and 52 developed scoliosis throughout the study. The median age of scoliosis was 17.1 years in the whole population, 17.1 years in the CSs-treated group, and 13.9 years in the CSs-naïve group (P = .18) (e-Fig 2, Table 2).

CSs Duration and Regimens

Sixty-six of 270 patients (24%) were in the CSs-daily group, 182 (67%) were in the CSs-intermittent group, and 22 (8%) were in the CSs-naïve group. In the cardiac cohort, 52 of 229 patients (23%) were in the CSs-daily group, 156 (68%) were in the CSs-intermittent group, and 21 (9%) were in the CSs-naïve group.

Thirty-seven boys (14%) stopped CSs (median age, 10.1 years; IQR, 5), including five in the CSs-daily

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

TABLE 2] Ambulatory Status and Scoliosis of the Study Population (N = 270)

Variable	No. (%)	Mean Age ± SD (y)
Ambulatory status		
Ambulant at baseline	263 (97.4)	6.0 ± 2.1
Not ambulant at baseline	7 (2.6)	11.5 ± 2.9
Variable	**No./Total No. (%)**	**Median Age at LoA (IQR) (y)**
Not ambulant at last follow-up	128/268 (47.8)	12.1 (10.0-14.5)
Daily	28/65 (43.1)	12.5 (10.0-15.7)
Intermittent	88/181 (48.6)	12.0 (10.0-14.0)
Naïve	12/22 (54.6)	10.5 (9.1-11.2)
Scoliosis at baseline	4/269 (1.5)	13.1 (1.0)
Variable	**No./Total No. (%)**	**Median (IQR)**
Scoliosis	57 (21.1)	17.1 (13.7[a])
Daily	7/66 (10.6)	…
Intermittent	44/182 (24.2)	15.5 (13.5[a])
Naïve	6/21 (28.6)	13.9 (12.7[a])
Scoliosis surgery	16/269 (5.9)	…
Daily	1/66 (1.5)	…
Intermittent	15/182 (8.2)	…
Naïve	0/21 (0)	…

Median age to events was estimated by Cox regression. Corticosteroid treatment: regimen used for ≥ 60% total corticosteroids treatment duration. IQR = interquartile range; LoA = loss of ambulation.
[a]Not possible to estimate.

group and their reasons were unavailable and 32 in the CSs-intermittent group. One stopped because of behavioral issues, one because of weight gain, and one because of BP increase; information was missing for the remainder. In the cardiac cohort, 33 patients stopped CSs.

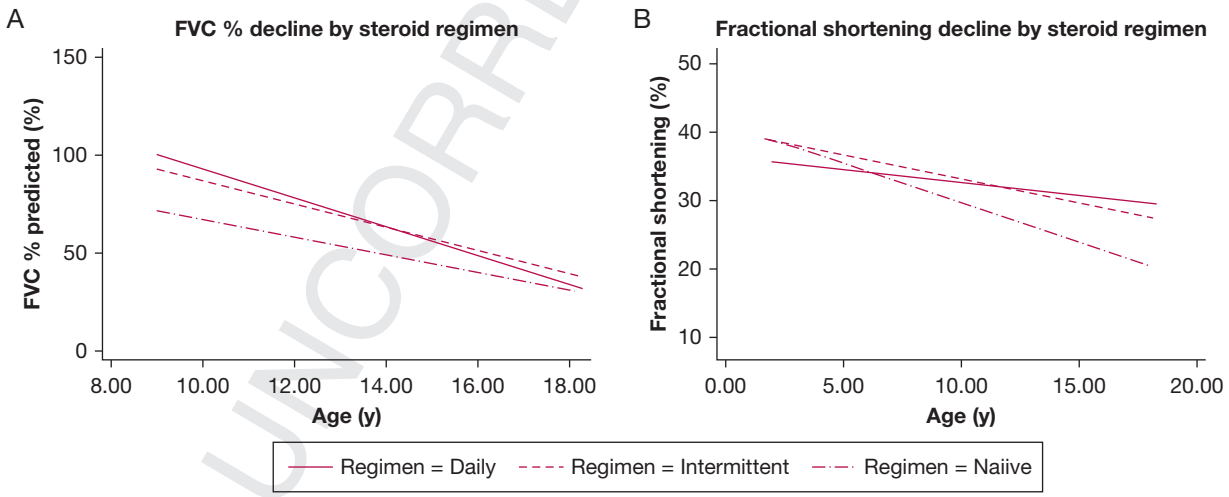

Figure 1 – *A-B, Slopes of annual respiratory and cardiac progression according to corticosteroids (CSs) regimen. A, FVC % predicted decline in CSs-daily, CSs-intermittent, and CSs-naïve patients with Duchenne muscular dystrophy (DMD). Linear population average model of respiratory function progression expressed as FVC % predicted according to CSs regimen after the age of 9 y. In the whole population, FVC % predicted declined linearly by 6.1% per year (95% CI, −6.6 to −5.6). FVC % predicted declined by 4.7% per year (95% CI, −6.6 to −2.8) in the CSs-naïve group. There were no differences in the yearly rate of decline between CSs-naïve and CSs-treated patients (P = .15). B, Left ventricular shortening fraction (LVFS%) decline in CSs-daily, CSs-intermittent, and CSs-naïve patients with DMD. Linear population average model of cardiac function progression expressed as LVFS % according to CSs regimen. In the whole population, LVFS% declined by 0.67% (95% CI, 0.55-0.79) per year. CSs-naïve boys had an LVFS% decline of 1.17% per year (95% CI, −1.55 to −0.79). Patients on any CSs progressed by 0.53% per year (95% CI, −0.67 to −0.40), slower than CS-naïve patients (P < .01). There was no difference in daily and intermittently treated patients (P = .59).*

Two-hundred and four of 270 patients (75%) were on prednisolone; 36 (13%) were on deflazacort for ≥ 60% of treatment. Twenty-five patients switched compounds, all from prednisolone to deflazacort.

Respiratory Status

Progression of FVC % Predicted and FVC: FVC % predicted slowly increased with age and then started declining linearly from 9 years of age. In the whole population, the yearly decline was by 6.1% per year (95% CI, 5.6-6.6). The CSs-daily group had the fastest FVC % predicted decline of 6.9% per year (95% CI, −7.7 to −6.0). These patients progressed by an extra 1% per year compared with the majority intermittent-CSs group. There was no difference between regimens (P = .27) (Fig 1A).

Data on absolute FVC progression according to CSs treatment are shown in e-Appendix 1. In the whole population, the mean age at peak FVC % predicted before declining was 9.7 ± 3.4 years. It was similar between regimens and in the CSs-treated group vs the CSs-naïve group. Conversely, the peak FVC % predicted value before the decline was significantly higher in the CSs-daily group (90.8%) than the CSs-intermittent group (83.9%, P < .01). The FVC % predicted, being affected by patients' height, was significantly higher in the CSs-daily group than the CSs-intermittent group, unlike absolute FVC. Because the CSs-daily group experienced a more severe height restriction (up to 1.8 cm per year[35]) compared with the CSs-intermittent group,[28] their FVC % predicted may be artifactually higher.

The CSs-naïve group had a FVC % predicted decline of 4.7% per year (95% CI, 2.8-6.6), not different than the CSs-treated group (P = .15), but the CSs-treated group peaked up to a significantly higher FVC % predicted than the CSs-naïve group (68.9%, P < .01).

Age at Respiratory End Points: Fifty-two patients fell to FVC % predicted < 50%. Twelve were in the CSs-daily group, 34 were in the CSs-intermittent group, and six were in the CSs-naïve group. The median age at FVC % predicted < 50% was similar (P = .86) between regimens (16.1 years in the CSs-daily group and 16.3 years in the CSs-intermittent group). The median age at FVC % predicted < 50% was significantly lower (P = .04) in those treated with deflazacort than those treated with prednisolone (15.4 vs 16.8 years, respectively; HR, 2.3; 95% CI, 1.03-5.31) (e-Fig 3A, Fig 2).

Absolute FVC fell < 1 L in 11 patients (4%): two of 66 (3%) were the CSs-daily group, six of 182 (3%) were in the CSs-intermittent group, and three of 22 (14%) were the CSs-naïve group. In the CSs-daily and CSs-intermittent groups, FVC fell < 1 L after 18 years of age.

Twenty of 270 patients (7%) required NIV. Five of 66 were in the CSs-daily group, 12 of 182 were in the CSs-intermittent group, and three of 22 were in the CSs-naïve group. Less than 25% of patients on any CSs regimen required NIV by 18 years of age (Fig 3).

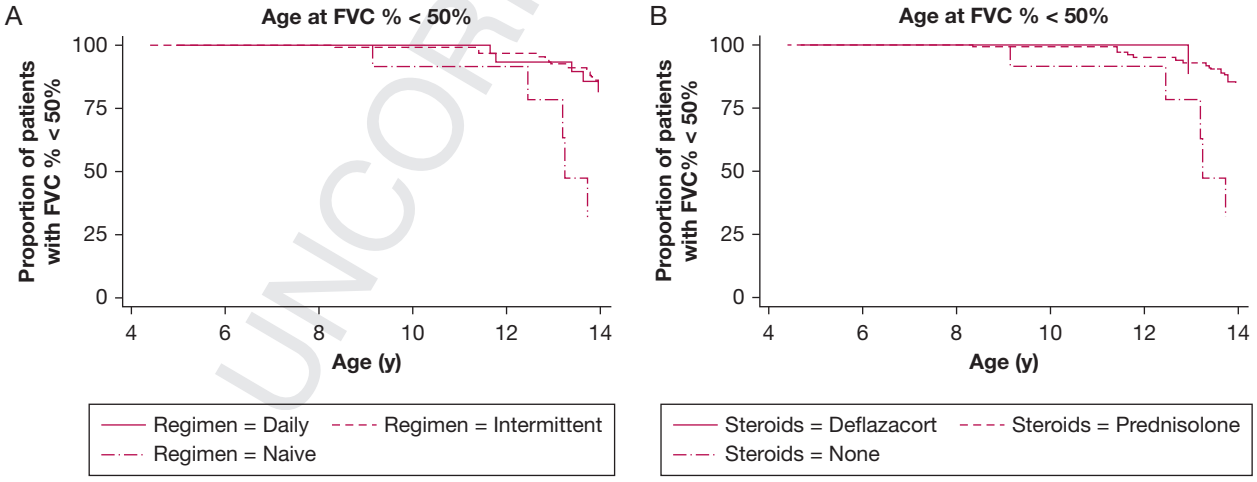

Figure 2 – *A-B, Time to respiratory failure defined as FVC % predicted < 50% according to CSs regimen and compound. A, Time to reach FVC % predicted < 50% according to regimen. Median age at FVC % predicted < 50% was 13.2 y in CSs-naïve patients. It was lower than CSs-daily (16.1 y, P < .01) and CSs-intermittent (16.3 y, P = .001) patients. Age at FVC % predicted < 50% was similar between the two CSs regimens (P = .86). B, Time to reach FVC % predicted < 50% according to CSs compound. The median age at FVC % predicted < 50% was significantly lower (P = .04) in those treated with deflazacort compared with prednisolone (15.4 vs 16.8 y, respectively; hazard ratio, 2.3; 95% CI, 1.03-5.31). See Figure 1 legend for expansion of abbreviation.*

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

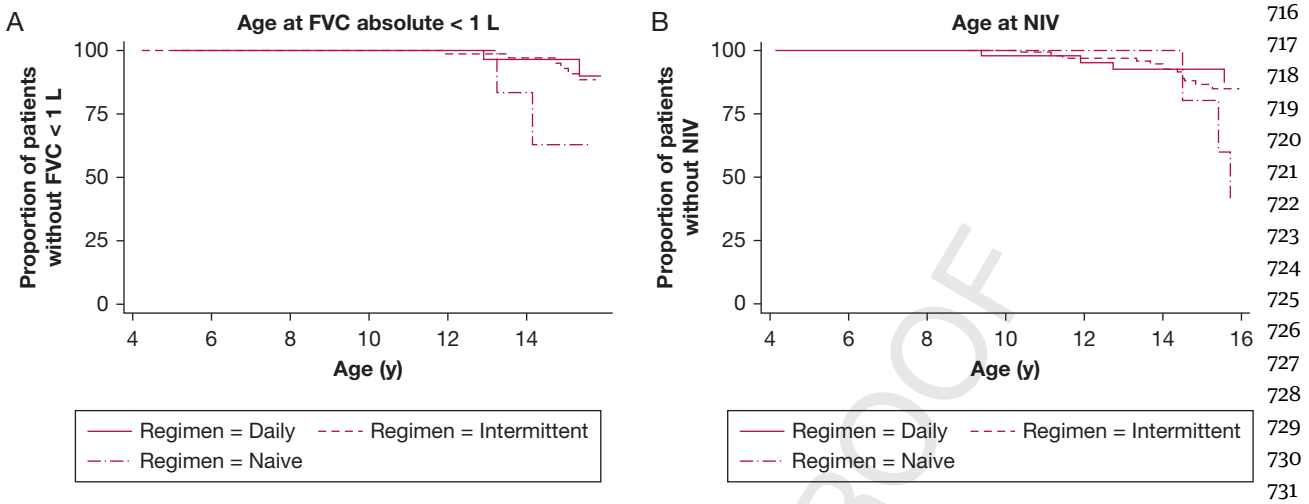

Figure 3 – *A-B, Time to respiratory clinically meaningful end points, absolute FVC < 1 L, and NIV requirement according to CSs regimen. A, Time to reach absolute FVC < 1 L. Eleven of 270 patients (4%) had absolute FVC < 1 L. Two of 66 patients (3%) were in the CSs-daily group, six of 182 patients (3%) were in the CSs-intermittent group, and three of 22 patients (14%) were in the CSs-naïve group. CSs-naïve patients reached absolute FVC < 1 L at a median age of 17 y, earlier than those in the CSs-daily (P = .04) and CSs-intermittent (P = .01) groups who fell < 1 L after 18 y. B, Time to NIV requirement. Twenty of 270 patients (7%) required NIV. Five of 66 patients (8%) were in the CSs-daily group, 12 of 182 (7%) were in the CSs-intermittent group, and three of 22 (14%) were in the CSs-naïve group. CSs-naïve boys required NIV at a median age of 15.7 y, whereas < 25% of patients on any CSs regimen required NIV at 18 y of age. NIV = noninvasive ventilation. See Figure 1 legend for expansion of other abbreviation.*

The CSs-naïve group reached FVC % predicted < 50% at a median age of 13.2 years and FVC < 1 L at a median age of 17 years, significantly earlier ($P < .01$ and $P < .05$, respectively) than the CSs-treated group. The CSs-naïve group required NIV at a median age of 15.7 years, earlier than the CSs-treated group.

Cardiac Status

Progression of LVFS%: Two-hundred and twenty-nine patients were included. The yearly decline of LVFS% was 0.67% per year (95% CI, 0.55-0.79; $P < .001$) in the whole population adjusted for age at baseline. Cardiac function decline was not different between CSs regimens ($P = .59$) (Fig 1B).

LVFS% yearly decline was 1.17% per year (95% CI, 0.79-1.55) in the CSs-naïve group and 0.53% per year (95% CI, 0.40-0.67) in the CSs-treated group ($P < .01$).

Age at Cardiomyopathy: Sixty patients (22%) had cardiomyopathy (LVFS% < 28%), six had it already at baseline and 54 developed it during the study. Ten were in the CSs-daily group, 41 were in the CSs-intermittent group, and nine were in the CSs-naïve group. The median age at cardiomyopathy was 16.6 years in the CSs-treated group, and this was similar between regimens ($P = .45$). The median age at cardiomyopathy for patients on prednisolone was 16.6 years. Less than 25% patients on deflazacort had cardiomyopathy by 18 years of age (HR, 0.74; 95% CI, 0.27-2.08). Age was not different ($P = .57$) according to CSs treatment (e-Fig 3B, Fig 4). The CSs-naïve group developed cardiomyopathy at 13.9 years of age (HR, 2.2; 95% CI, 1.1-4.6), earlier ($P < .05$) than the CSs-treated group (see e-Appendix 1 for further details on cardiac medications).

Genotype/Phenotype Correlation

Children amenable to exon 44 skipping had a slower respiratory decline (4.5% per year) than patients not amenable to skipping of exon 44 ($P < .05$). Respiratory decline was not different in patients amenable to skip 45, 51, and 53 compared with the remaining patients. There was no difference in decline of cardiac function according to amenability to skip of any exon.

Eighteen (7%) and 28 (10%) patients had mutations causing Dp71 and Dp116 shorter dystrophin isoform deficiency. FVC % predicted < 50%, absolute FVC < 1 L, age at NIV, and cardiomyopathy were similar in patients lacking Dp71 and Dp116 isoforms compared with the patients expressing them.

Discussion

CSs are the current standard mutation-independent treatment for DMD. The impact of CSs regimen and compounds on long-term cardiorespiratory function is unknown.

In a previous study, the comparison between deflazacort and prednisolone on respiratory function in 60 patients with DMD (5-24 years of age) found no differences in yearly progression of FVC % predicted according to

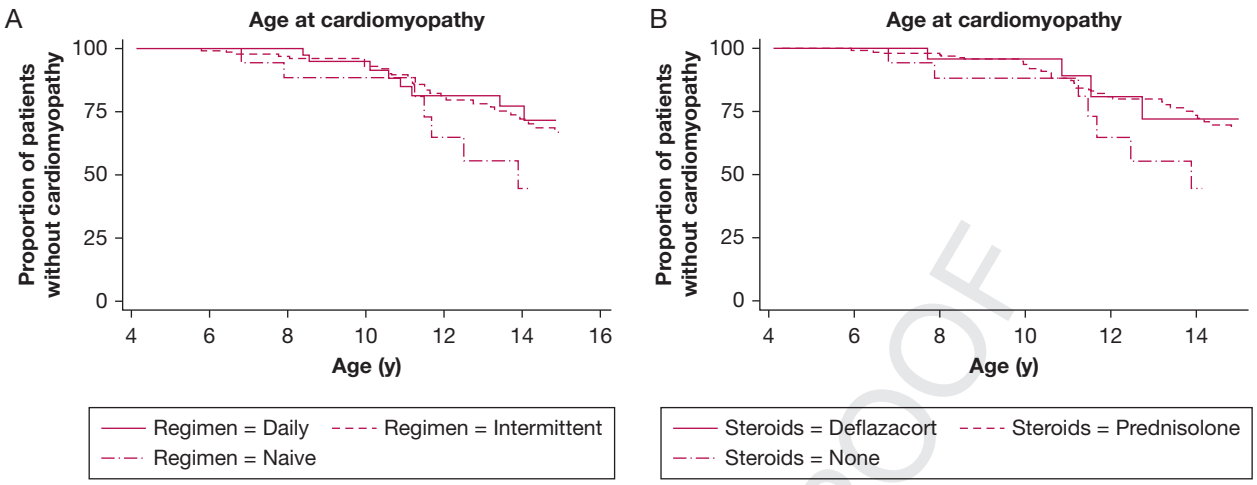

Figure 4 – *A-B, Time to cardiomyopathy defined as left ventricular shortening fraction < 28% according to CSs regimen and compound. A, Age at onset of cardiomyopathy according to regimen. Median age was 13.9 y in CSs-naïve boys and 16.6 y in CSs-treated boys (P < .05). There were no differences in age at cardiomyopathy between CSs regimens (P = .45). B, Age at onset of cardiomyopathy according to CSs compound. The median age at FVC % predicted < 50% was not different according to CSs treatment (P = .57). The median age at cardiomyopathy for patients on prednisolone was 16.6 y. Less than 25% patients on deflazacort had cardiomyopathy by 18 y of age (hazard ratio, 0.74; 95% CI, 0.27-2.08). Patients who started ACE-inhibitors (four of 82) and beta-blockers (three of 37) prior to the onset of cardiomyopathy were included. See Figure 1 legend for expansion of abbreviation.*

treatment.[12] Other studies have instead focused on the impact of CSs on delaying respiratory deficiency compared with no treatment, providing controversial results. The respiratory decline in DMD seems in fact affected by variables only partially addressed by CSs, as age, ambulation, and additional comorbidities (poor swallowing and ineffective cough) affecting intrinsically the lung. In the placebo arm of the DELOS trial, nonambulant CSs-naïve patients with DMD (n = 33; mean age, 15 years) had a similar FVC % predicted decline > 8% over 1 year as those on previous CSs.[9,36] In 91 nonambulant men with DMD (mean age, 16.8 years), respiratory function declined at a similar rate in CSs-treated and CSs-naïve patients.[10] In younger patients with DMD, instead, CSs positively acted on lung function by reaching higher peak FVC % predicted than CSs-naïve patients before the onset of respiratory decline. In 397 patients with DMD 7 to > 20 years of age, the FVC % predicted remained significantly higher in boys treated with CSs than CSs-naïve patients at all ages. We can postulate that CS's positive effect on diaphragmatic function led to greater lung function.[37] Although in the age range of 7 to 10 years, FVC % predicted declined slower in the CSs-treated group than the CSs-naïve group (0.69% vs 5.9%, respectively); FVC % predicted yearly progression was similar in boys 10 to 18 years of age (5.44% vs 6.06%, respectively).[15] All these results suggest that CSs delay the onset of respiratory decline and the achievement of respiratory milestones (FVC < 1 L) but do not slow down its progression once decline has started.[4,15]

Because the standards of care for DMD have changed in the last years and virtually no CSs-naïve patients exist anymore, the main aim of our work was to identify the impact of different CSs regimens and compounds on yearly FVC % predicted progression. In the population, patients with CS-daily-treated DMD reached a peak FVC % predicted 10% higher than the CS-intermittent group and 22% higher than the CSs-naïve group predicted before the decline (e-Fig 4). CSs-daily and CSs-intermittent groups led to a similar extent of delay in FVC % predicted < 50% and in NIV requirement of, respectively, 3 and > 2 years compared with the CSs-naïve group. In addition, our results show that patients on deflazacort reached FVC % predicted < 50% over 1 year earlier than those on prednisolone (15.4 vs 16.8 years, respectively). Previous reports on ambulation and timed motor outcomes, carried out over a shorter period and/or on younger patients, found a more preserved function in DMD treated with deflazacort.[38-40] Our data suggest that deflazacort is effective on respiratory function in the short/medium term but that its long-term efficacy might be inferior compared with prednisolone in the late stages, probably as a result of the more severe growth restriction induced by this drug.

The existing studies on cardiac function in DMD have demonstrated the beneficial role of daily CSs over no treatment. A cross-sectional study demonstrated significantly higher LVFS% in CSs-treated (n = 48) vs age-matched CSs-naïve boys with DMD (n = 63).[8]

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

Daily CSs significantly reduced LVFS% decline over 5 years in CSs-treated (n = 14) vs CSs-naïve (n = 23) boys with DMD.[7] CSs duration delayed cardiomyopathy in DMD by 4% per year (n = 462).[6] Finally, daily CSs treatment was associated with fewer heart failure-related deaths (0% vs 22%) and a slower LVFS% decline (−0.32% vs −0.65%) in 63 CSs-treated vs 23 CSs-naïve patients with DMD.[5] CSs duration was associated with lower age-related fibrosis at cardiac MRI.[41] In 174 boys with DMD, cardiomyopathy was associated with age and clinical stage, but not with CSs treatment.[42] Our long-term data on a wide DMD population confirm the cardioprotective effect of CSs,[43] adding that CSs, particularly daily, delayed the onset of cardiomyopathy through slowing down cardiac decline. To our knowledge, our findings showed for the first time that the cardioprotective effect was longer-lasting in CSs-daily vs CSs-intermittent patients and that, in contrast with respiratory data, patients on deflazacort developed cardiomyopathy later than those on prednisolone (> 18 vs 16.6 years). CSs-naïve boys with DMD developed cardiomyopathy significantly younger than CSs-treated boys (13.9 vs 16.6 years, respectively).

These results support the administration of CSs after LoA in DMD. However, the side effects caused by the prolonged use of CSs reported by other studies within the UK NorthStar Network should not be underestimated. Daily CSs had stronger effects than intermittent CSs on ambulation, but negatively affected behavior, growth, and BMI.[28] Similarly, CSs-daily patients with DMD (deflazacort) had a significantly higher bone fractures rate than CSs-intermittent patients. Of note, vertebral fractures further affect height.[44]

Long-term cardiorespiratory trajectories according to amenability to exon skipping have implications for ongoing trials and will help the design of future studies. Patients amenable to exon 44 skip have better walking distance and slower decline than others,[26] and lose ambulation later.[25,27] We demonstrate for the first time that these patients also have a slower respiratory function decline ($P < .05$). There were no significant differences in time to cardiomyopathy or respiratory failure in boys lacking Dp71 (6%) or Dp116 (9%) compared with those expressing them. We had hypothesized that a Dp71 deficiency could have a protective role in dystrophic heart, and previous studies have suggested a protective role of Dp116 deficiency. The overexpression of AAV-mediated Dp71 worsened *mdx* mouse phenotype by competing with utrophin in its binding to dystrophin-associated protein complex.[45] The previously reported protective role of Dp116 deficiency on heart function in 181 boys with DMD was not supported by our results on a wider cohort.[19]

In the population, 10.6% of CSs-daily patients, 24.2% of CSs-intermittent patients, and 27.3% of CSs-naïve patients developed scoliosis. The small numbers of events did not allow a time-to-event analysis. The percentage of scoliosis in the CSs-naïve patients is lower than previously reported[46] because of our more stringent definition. Most CSs-naïve patients were enrolled in the first 5 years of the study. A more proactive indication to spinal surgery and the availability of new techniques in recent years may explain why in the cohort none of the CSs-naïve patients underwent surgery by 18 years of age.

Our long-term real-world data are novel and were collected over > 5 years in a single center within the NorthStar UK database. The only ongoing randomized trial, the FOR-DMD,[47] will address the question of which regimen is more effective. Patients were enrolled at 4 to 7 years of age. They could still be too young to reach cardiorespiratory end point.

The main limitations of this study are its retrospective and monocentric design. The imbalance in the cohort sample size, with lower numbers of CSs-naïve boys, might have affected our results. We have included assessments only conducted in a single tertiary site by the same highly skilled operators to limit the risk of bias, which is however inevitable. The collection of long-term data over 17 years was potentially affected by changes in the standard of care in DMD. In the most recent 7 years of study, CSs were stopped after LoA in 14% vs 42% in the previous 7 years. When we ran sensitivity analyses adjusting for date of visit in the mixed models, this had minimal, nonsignificant impact on estimated coefficients of interest; therefore, we presented results for models without this factor. The use of the CSs regimen administered over most of the study to minimize the weight of switchers has previously proven effective.[28] The use of arm span used as surrogate of height after LoA could have affected the FVC % predicted at the time point of switch. However, the results on FVC absolute matched with those of FVC % predicted. The use of cardiac medications could have potentially influenced the cardiac progression, but > 90% of patients started cardiac medication after the diagnosis of cardiomyopathy.

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891

Interpretation

Our data confirm the long-term beneficial effect of corticosteroids on respiratory and cardiac function in 270 patients with DMD, irrespective of regimen. CSs-daily-treated DMD reached a significantly higher FVC % predicted than CSs-intermittent-treated DMD before decline, but a similar yearly FVC % predicted decline. There was no difference in the age at clinically meaningful respiratory thresholds (FVC % predicted < 50% and NIV requirement) according to CSs regimen. The CSs-daily and CSs-intermittent groups had a similar rate of cardiac decline that resulted in a delayed onset of cardiomyopathy (2.7 years) compared with the CSs-naïve group.

Further work is needed to evaluate the differential role of CSs in older nonambulant patients, particularly in view of the evidence for their positive effects on cardiac function.

Acknowledgments

Author contributions: F. M. takes responsibility for the content of the manuscript, including the data and analysis. F. T. designed and conceptualized the study, analyzed the data, and drafted the manuscript for intellectual content. J. D. and C. G. T. played a major role in the acquisition of data and design of the study. D. R. designed and conceptualized the study and analyzed the data. K. M., P. M., A. S., S. R., R. Q., M. B., M. F., C. W., E. C., F. A., and A. M. interpreted the data and revised the manuscript for intellectual content. M. R. played a major role in the acquisition of data. F. M. designed and conceptualized the study and revised the manuscript for intellectual content.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: F. M. reports grants from Sarepta, grants from Wave, grants from PTC, personal fees from Roche, personal fees from Pfizer, and personal fees from Sarepta, outside the submitted work. None declared (F. T., J. D., C. G. T., D. R., K. M., P. M., A. S., S. R., R. Q., M. R., M. B., M. F., C. W., E. C., F. A., A. M.).

Role of sponsor: The views expressed in this manuscript are those of the authors and not necessarily of the NIHR.

Other contributions: We thank the GOSH physiotherapy team for their role in the assessment of motor function in patients with DMD.

Additional information: The e-Appendix and e-Figures can be found in the Supplemental Materials section of the online article.

References

1. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4):347-361.
2. McNally EM, Kaltman JR, Benson DW, et al. Contemporary cardiac issues in Duchenne muscular dystrophy. Working Group of the National Heart, Lung, and Blood Institute in collaboration with Parent Project Muscular Dystrophy. *Circulation*. 2015;131(18):1590-1598.
3. Gloss D, Moxley RT III, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(5):465-472.
4. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet*. 2018;391(10119):451-461.
5. Schram G, Fournier A, Leduc H, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. *J Am Coll Cardiol*. 2013;61(9):948-954.
6. Barber BJ, Andrews JG, Lu Z, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. *J Pediatr*. 2013;163(4):1080-1084.e1.
7. Markham LW, Kinnett K, Wong BL, et al. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2008;18(5):365-370.
8. Markham LW, Spicer RL, Khoury PR, et al. Steroid therapy and cardiac function in Duchenne muscular dystrophy. *Pediatr Cardiol*. 2005;26(6):768-771.
9. Buyse GM, Voit T, Schara U, et al. Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. *Lancet*. 2015;385(9979):1748-1757.
10. Connolly AM, Florence JM, Zaidman CM, et al. Clinical trial readiness in non-ambulatory boys and men with duchenne muscular dystrophy: MDA-DMD network follow-up. *Muscle Nerve*. 2016;54(4):681-689.
11. NCT01027884.
12. Mayer OH, Finkel RS, Rummey C, et al. Characterization of pulmonary function in Duchenne muscular dystrophy. *Pediatr Pulmonol*. 2015;50(5):487-494.
13. Henricson EK, Abresch RT, Cnaan A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. *Muscle Nerve*. 2013;48(1):55-67.
14. Connolly AM, Malkus EC, Mendell JR, et al. Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy. *Muscle Nerve*. 2015;51(4):522-532.
15. McDonald CM, Gordish-Dressman H, Henricson EK, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: long-term natural history with and without glucocorticoids. *Neuromuscul Disord*. 2018;28(11):897-909.
16. Bourke JP, Watson G, Muntoni F, et al. Randomised placebo-controlled trial of combination ACE inhibitor and beta-blocker therapy to prevent cardiomyopathy in children with Duchenne muscular dystrophy? (DMD Heart Protection Study): a protocol study. *BMJ Open*. 2018;8(12):e022572.
17. EudraCT2007-005932-10.
18. Matsuo M, Awano H, Matsumoto M, et al. Dystrophin Dp116: a yet to be investigated product of the duchenne muscular dystrophy gene. *Genes (Basel)*. 2017;8(10):251.
19. Yamamoto T, Awano H, Zhang Z, et al. Cardiac dysfunction in Duchenne muscular dystrophy is less frequent in patients with mutations in the dystrophin Dp116 coding region than in other regions. *Circ Genom Precis Med*. 2018;11(1):e001782.
20. Byers TJ, Lidov HG, Kunkel LM. An alternative dystrophin trascript specific to peripheral nerve. *Nat Genet*. 1993;4(1):77-81.
21. Sadoulet-Puccio HM, Kunkel LM. Dystrophin and its isoforms. *Brain Pathol*. 1996;6(1):25-35.
22. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol*. 2003;2:731-740.
23. Aragon J, Gonzalez-Reyes M, Romo-Yanez J, et al. Dystrophin Dp71 isoforms are differentially expressed in the mouse brain and retina: report of new alternative splicing and a novel nomenclature for Dp71 isoforms. *Mol Neurobiol*. 2018;55(2):1376-1386.

24. Tadayoni R, Rendon A, Soria-Jasso LE, et al. Dystrophin Dp71: the smallest but multifunctional product of the Duchenne muscular dystrophy gene. *Mol Neurobiol*. 2012;45(1):43-60.
25. Bello L, Morgenroth LP, Gordish-Dressman H, et al. DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. *Neurology*. 2016;87(4):401-409.
26. Brogna C, Coratti G, Pane M, et al. Long-term natural history data in Duchenne muscular dystrophy ambulant patients with mutations amenable to skip exons 44, 45, 51 and 53. *PLoS One*. 2019;14(6):e0218683.
27. Ricotti V, Ridout DA, Pane M, et al. The NorthStar Ambulatory Assessment in Duchenne muscular dystrophy: considerations for the design of clinical trials. *J Neurol Neurosurg Psychiatry*. 2016;87(2):149-155.
28. Ricotti V, Ridout DA, Scott E, et al. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *J Neurol Neurosurg Psychiatry*. 2013;84(6):698-705.
29. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319-338.
30. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
31. Hull J, Aniapravan R, Chan E, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. *Thorax*. 2012;67(suppl 1):i1-i40.
32. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. *Am J Respir Crit Care Med*. 2004;170(4):456-465.
33. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006;7(2):79-108.
34. Spurney CF, McCaffrey FM, Cnaan A, et al. Feasibility and reproducibility of echocardiographic measures in children with muscular dystrophies. *J Am Soc Echocardiogr*. 2015;28(8):999-1008.
35. Lamb MM, West NA, Ouyang L, et al. Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. *J Pediatr*. 2016;173:207-213.e3.
36. Meier T, Rummey C, Leinonen M, et al. Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy. *Neuromuscul Disord*. 2017;27(4):307-314.
37. LoMauro A, Romei M, Gandossini S, et al. Evolution of respiratory function in Duchenne muscular dystrophy from childhood to adulthood. *Eur Respir J*. 2018;51(2).
38. Bello L, Gordish-Dressman H, Morgenroth LP, et al. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology*. 2015;85(12):1048-1055.
39. Shieh PB, McIntosh J, Jin F, et al. Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: a post HOC analysis from the ACT DMD trial. *Muscle Nerve*. 2018;58(5):639-645.
40. McDonald CM, Sajeev G, Yao Z, et al. Deflazacort vs prednisone treatment for Duchenne muscular dystrophy: a meta-analysis of disease progression rates in recent multicenter clinical trials. *Muscle Nerve*. 2020;61(1):26-35.
41. Tandon A, Villa CR, Hor KN, et al. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. *J Am Heart Assoc*. 2015;4(4).
42. Spurney C, Shimizu R, Morgenroth LP, et al. Cooperative International Neuromuscular Research Group Duchenne Natural History Study demonstrates insufficient diagnosis and treatment of cardiomyopathy in Duchenne muscular dystrophy. *Muscle Nerve*. 2014;50(2):250-256.
43. Raman SV, Cripe LH. Glucocorticoid therapy for Duchenne cardiomyopathy: a Hobson's choice? *J Am Heart Assoc*. 2015;4(4).
44. Joseph S, Wang C, Bushby K, et al. Fractures and linear growth in a nationwide cohort of boys with Duchenne muscular dystrophy with and without glucocorticoid treatment: results from the UK NorthStar Database. *JAMA Neurol*. 2019;76(6):701-709.
45. Gardner KL, Kearney JA, Edwards JD, et al. Restoration of all dystrophin protein interactions by functional domains in trans does not rescue dystrophy. *Gene Ther*. 2006;13(9):744-751.
46. Houde S, Filiatrault M, Fournier A, et al. Deflazacort use in Duchenne muscular dystrophy: an 8-year follow-up. *Pediatr Neurol*. 2008;38(3):200-206.
47. Guglieri M, Bushby K, McDermott MP, et al. Developing standardized corticosteroid treatment for Duchenne muscular dystrophy. *Contemp Clin Trials*. 2017;58:34-39.

FLA 5.6.0 DTD ■ CHEST3136_proof ■ 5 July 2020 ■ 5:56 am ■ EO: CHEST-19-2891