Comparison of Pulmonary Function Decline in Steroid-Treated and Steroid-Naïve Patients with Duchenne Muscular Dystrophy

Hemant Sawnani, MD[1,2], Paul S. Horn, PhD[2,3], Brenda Wong, MD[2,3], Andrew Darmahkasih[4], Irina Rybalsky, MD, PhD[2,3], Karen C. Shellenbarger, APRN[3], Cuixia Tian, MD[2,3], Meilan M. Rutter, MB, BCh, FRACP[2,5], Narong Simakajornboon, MD[1,2], Raouf Amin, MD[1,2], Neepa Gurbani, DO[1,2], John Pascoe, MD[1,2], Carolyn Burrows, APRN[1], Sonia Khirani, PhD[6,7], Alessandro Amaddeo, MD, PhD[6], and Brigitte Fauroux, MD, PhD[6]

Objective To describe and compare the lung function decline in patients with Duchenne muscular dystrophy on glucocorticoid therapy in contrast with glucocorticoid-naïve patients, and to define the deciles of pulmonary decline in glucocorticoid-treated patients.

Study design This retrospective study examined lung function of patients with Duchenne muscular dystrophy over 6 years of age followed between 2001 and 2015 at 2 centers—glucocorticoid-treated patients in Cincinnati, Ohio, and glucocorticoid-naïve patients in Paris, France. Forced vital capacity (FVC, FVC%), forced expiratory volume in 1 second, maximal inspiratory pressure, maximal expiratory pressure, and peak expiratory flow data were analyzed. Only FVC data were available for the French cohort.

Results There were 170 glucocorticoid-treated patients (92%), 5 patients (2.7%) with past glucocorticoid use, and 50 French glucocorticoid-naïve patients. The peak absolute FVC was higher and was achieved at earlier ages in glucocorticoid-treated compared with glucocorticoid-naïve patients (peak FVC, 2.4 ± 0.6 L vs 1.9 ± 0.7 L; $P < .0001$; ages 13.5 ± 3.0 years vs 14.3 ± 2.8 years; $P = .03$). The peak FVC% was also higher and was achieved at earlier ages in glucocorticoid-treated patients (peak FVC%, 105.1 ± 25.1% vs 56 ± 20.9%; $P < .0001$; ages 11.9 ± 2.9 years vs 13.6 ± 3.2 years; $P = .002$). Rates of decline for both groups varied with age. Maximal rates of decline were 5.0 ± 0.26% per year (12-20 years) for glucocorticoid-treated and 5.1 ± 0.39% per year for glucocorticoid-naïve patients (11-20 years; $P = .2$). Deciles of FVC% decline in glucocorticoid-treated patients show that patients experience accelerated decline at variable ages.

Conclusions These data describe nonlinear rates of decline of pulmonary function in patients with Duchenne muscular dystrophy, with improved function in glucocorticoid-treated patients. FVC% deciles may be a useful tool for clinical and research use. *(J Pediatr 2019;210:194-200)*.

Duchenne muscular dystrophy (DMD; OMIM 310200) is an X-linked inherited disease that manifests progressive muscle degeneration from deficiency of dystrophin.[1,2] Loss of respiratory muscle strength leads to respiratory morbidity from recurrent atelectasis and pneumonia, sleep-disordered breathing and, finally, chronic hypercapneic respiratory failure.[3] Respiratory failure is the cause of death in the majority of patients with DMD, although the time of death is variable. Although this may hold true for patients with challenged access to relevant medical expertise (as in poorer developing countries), mortality seems to be related to progressive cardiomyopathy for patients with adequate treatment and institution of assisted ventilation.[4]

The initiation of noninvasive ventilation proved pivotal in prolonging median survival from 19 years for patients not on noninvasive ventilation patients to a median survival of 27 years for patients on noninvasive ventilation,[5] although concomitant cardiomyopathy has been shown to significantly shorten life expectancy.[6] Since the earliest reported benefits of glucocorticoid therapy in DMD,[7] subsequent studies demonstrated rapid early improvement and/or preservation of muscle strength, with a delay in the loss of ambulation of up to 2 to 3 years longer than for nontreated patients.[8-13] Glucocorticoids have also been credited with significant reduction in all-cause mortality.[14] Favorable outcomes despite side effects are possible with coordinated, patient-centered interdisciplinary care[15] wherein strict vigilance

ATS	American Thoracic Society
DMD	Duchenne muscular dystrophy
ERS	European Respiratory Society
FVC	Forced vital capacity
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
PFT	Pulmonary function test

From the [1]Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center; [2]Department of Pediatrics, University of Cincinnati College of Medicine; [3]Division of Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]Wayne State University School of Medicine, Detroit, MI; [5]Division of Endocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [6]Pediatric Non-invasive Ventilation and Sleep Unit, Necker University Hospital, Paris; and [7]ASV Santé, Gennevilliers, France

Funded by the Cincinnati Children's Research Foundation. The authors declare no conflicts of interest.

Portions of this study were presented as a poster at the International Conference of the American Thoracic Society, May 13-18, 2016, San Francisco, California.

https://doi.org/10.1016/j.jpeds.2019.02.037

for side effects and aggressive pulmonary management are integral to the care plan.

Obtaining acceptable and reproducible lung function data in neuromuscular populations remains a challenge,[16] although less stringent criteria have been suggested.[17,18] Mayer et al showed that the use of glucocorticoid therapy was associated with nearly linear yearly decline in forced vital capacity (FVC%) of about 5% between 5 and 24 years of age.[18] Data from the longitudinal Cooperative International Neuromuscular Research Group Duchenne natural history study revealed that glucocorticoid therapy slowed the rate of FVC% decline in 7.0- to 9.9-year-old boys. It was also shown that glucocorticoid-treated boys with DMD experienced a nonlinear rate of pulmonary decline, with a maximum yearly decline of FVC% of 5.4%.[19] The authors described differential rates of pulmonary decline based on age brackets.[19] This, however, assumes that all patients in the same age range decline at a similar rate. The heterogeneity in rates of decline of motor and respiratory function in DMD[20] suggests that patients lose ambulation at different ages. It is conceivable that the point of accelerated pulmonary decline will also vary, and this could affect trial design and outcomes negatively.

The purpose of this study was to compare the onset and rates of lung function decline in boys with DMD managed with and without glucocorticoid therapy. We hypothesized that glucocorticoid therapy will delay and slow the rate of pulmonary decline. We also generated deciles of FVC% decline to describe the ages at which accelerated decline occurs and propose that the preservation of vital capacity could be considered an acceptable therapeutic outcome.

Methods

This retrospective study examined lung function data of patients with DMD (confirmed by genetic testing and/or muscle biopsy) older than 6 years of age from the neuromuscular centers at Cincinnati Children's Hospital (Cincinnati, Ohio) and Trousseau University Hospital (Paris, France). Patients had at least 2 clinic visits between 2001 and 2015. Only those with complete records were included in the study. Data from patients unable to perform more than 2 acceptable and repeatable spirometry tests and tests that were not within 5% agreement of each other, in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria,[21] were excluded. The Cincinnati patients were mostly glucocorticoid treated (daily prednisone or deflazacort) and those from Paris were glucocorticoid naïve. Patients who had stopped glucocorticoid therapy after any length of treatment for more than 1 month were considered past users of glucocorticoids. Exclusion criteria included recent spine surgery (within the preceding 6 months) and invasive ventilation via tracheostomy. Each center's institutional review board approved the study (Cincinnati Children's Hospital Medical Center IRB 1, Study 2010-1881; Institutional Review Board of the French Learned Society for Respiratory Medicine [Société de Pneumologie de Langue Francaise]).

At Cincinnati, pulmonary function tests (PFTs) included spirometry, maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP), and peak cough flow. At the French center, only FVC data were available and used for the present study. All PFTs were performed by qualified respiratory therapists following ATS/ERS standards. Tests were conducted in the upright, sitting position over 30-60 minutes to allow for recovery time. Respiratory muscle strength testing was performed before spirometry. Standing heights were measured with a calibrated wall-mounted stadiometer. For patients who were unable to stand, arm spans were measured.[22,23] For patients who were unable to stand and who developed upper extremity contractures, heights for the calculation of predicted PFT values were estimated from measurement of ulna lengths.[24] For each patient, the same consistent method of measurement was used over time (unless a transition was dictated by a change in their ambulatory status and/or development of contractures) for the calculation of their predicted PFT values and checked for acceptability and accuracy by clinicians to ensure valid longitudinal comparisons.

Statistical Analyses

Data from the US cohort with past-glucocorticoid were too few to provide reliable information; data from glucocorticoid-naïve patients from the US and France were combined for analyses. We examined for age-related changes in rates of disease progression to assess pulmonary decline over the follow-up period. By examining many pairs of age cut-points, as well as model-fitting criteria, cut-points at ages 12 and 18 years were determined most reasonable for glucocorticoid-treated patients. The specific cut-points of 12 and 18 years were chosen for the piecewise linear regression based on clinical experience/expertise and informed by statistical fit measures; specifically, the (corrected) Akaike information criterion and log likelihood. There was no difference between cut-point pairs of 12 and 18 years or 11 and 17 years. These were all within 0.1% of each other with respect to Akaike information criterion and log likelihood. Piecewise linear regression with knots at 12 and 18 years of age was used with age at the time of the clinical visit as the independent variable, lung function measurements as the response, and the patient as the random effect. Slope estimates were considered statistically significant if the P value was less than .05.

Decile curves were derived using a linear mixed model with radial smoothing. The within-patient covariance structure was the identity matrix; in other words, longitudinal data were treated as independent to generate the fitted percentile curves.[25]

Results

US Cohort

Of 416 patients with DMD reviewed at the Cincinnati Children's Hospital Medical Center, 184 patients met criteria

for more than 2 acceptable and repeatable spirometry tests. There were 170 glucocorticoid-treated patients (glucocorticoid group with 847 PFTs), 9 glucocorticoid-naïve patients (with 59 PFTs), and 5 past use of glucocorticoid patients (with 15 PFTs), yielding a total of 921 PFTs. Demographic data are shown in Table I (available at www.jpeds.com). The FVC data of the glucocorticoid-naïve patients from the US cohort were combined with the FVC data from the French cohort. There were 84 ambulatory patients (45.6%) and all were glucocorticoid treated. The mean ages (±SD) at loss of ambulation were: glucocorticoid, 12.02 ± 2.96 years; past glucocorticoid use, 12.08 ± 4.08 years; and glucocorticoid-naïve patients, 9.41 ± 1.48 years.

French Cohort

The 41 French glucocorticoid-naïve patients provided 101 FVC tests (Table I). As a result of examining many pairs of age cut-points, as well as a model-fitting criterion, different age cut-points were identified for various PFT measures, depending on their respective trajectories (Table II). These age cut-points corresponded with the ages at which the rates of decline of each PFT measure exhibited relatively greater rates of change.

Table II. Rates of decline of pulmonary function of the glucocorticoid-treated and glucocorticoid-naïve (US and French cohorts combined) DMD patients*

Glucocorticoid treated (n = 170)			Glucocorticoid naïve (n = 50)		
Age, y	**Estimate**	***P* value**	**Age, y**	**Estimate**	***P* value**
FVC, L					
≤12	0.12 ± 0.01	<.0001	≤9	0.81 ± 0.26	.0018
12 to ≤18	0.0004 ± 0.01	.95	9 to ≤15	0.04 ± 0.02	.04
>18	−0.07 ± 0.01	<.0001	>15	−0.21 ± 0.01	<.0001
FVC%					
≤12	−1.63 ± 0.44	<.0001	≤9	−2.27 ± 8.27	.78
12 to ≤18	−6.31 ± 0.27	<.0001	9 to ≤11	−1.50 ± 2.08	.47
18 <	−2.43 ± 0.42	<.0001	>11	−5.49 ± 0.29	<.0001
FEV_1%					
≤12	−2.13 ± 0.44	<.0001			
12 to ≤18	−6.49 ± 0.27	<.0001			
>18	−1.86 ± 0.43	<.0001			
MIP%					
≤10	−2.24 ± 1.39	.11			
10 to ≤16	−5.88 ± 0.45	<.0001			
>16	−5.60 ± 4.83	.25			
MEP%					
≤12	−2.64 ± 0.74	.0004			
12 to ≤16	−6.68 ± 0.70	<.0001			
>16	−3.59 ± 5.39	.51			
PEF/L/min					
≤11	0.24 ± 0.03	<.0001			
11 to ≤17	0.09 ± 0.01	<.0001			
>17	−0.07 ± 0.02	.0003			
PEF%					
≤9	−2.15 ± 1.57	.17			
9 to ≤15	−3.39 ± 0.26	<.0001			
>15	−2.07 ± 0.27	<.0001			

FEV$_1$, Forced expiratory volume in 1 second; *PEF*, Peak Expiratory Flow.
*Available data for the French glucocorticoid-naïve group was limited to vital capacity data.

Absolute FVC

For the glucocorticoid-treated group, absolute FVC increased over the first decade and plateaued between the ages of 12 and 18 years (Table II and Figure 1, A). For the glucocorticoid-naïve group, the absolute FVC values increased before 9 years and plateaued between 9 and 15 years of age, before declining after 15 years of age (Table II and Figure 1, A). The durations of the plateau phases were similar between the groups. The glucocorticoid-treated patients achieved significantly higher peak FVC (absolute and FVC%) values than the glucocorticoid-naïve patients, and at significantly younger ages (Table III; available at www.jpeds.com).

FVC%

For the glucocorticoid-treated group, the FVC% decreased linearly until the age of 12 years of age, with accelerated decline observed between the ages of 12 and 18 years of age (Table II and Figure 1, B). The rate of decline remained consistently significant thereafter. The glucocorticoid-naïve patients from both centers collectively revealed best-fit cut-points of 9 and 11 years of age, with a significant change in the linear annual rate of FVC% decline after the age of 11 years (Table II and Figure 1, B). To compare the maximal rates of FVC% decline in both groups, the glucocorticoid-treated group was limited to the age of 20 years to match the glucocorticoid-naïve group. At the age intervals encompassing maximal FVC% decline, the glucocorticoid-treated (12-20 years of age) and the glucocorticoid-naïve (11-20 years of age) groups declined at similar rates (5.90 ± 0.26% vs 5.08 ± 0.39% per year; $P = .08$).

FVC% Stratification

Decile curves were derived using all observations of glucocorticoid-treated patients. Table IV provides the estimated deciles for each age between the ages of 6 and 24 years. The FVC% declined with age, as expected, with the steepest rate of decline occurring in the early through the late teenage years (Figure 2).

Forced Expiratory Volume in 1 Second

For the glucocorticoid-treated group, the forced expiratory volume in 1 second declined linearly until the age of 12 years, with accelerated decline between the ages of 12 and 18 years (Table II and Figure 3, A [available at www.jpeds.com]).

Peak Expiratory Flow Rate

For the glucocorticoid-treated group, the peak expiratory flow rate decreased over the entire observed age range. The annual rates of decline of peak expiratory flow rate reached significance after the age of 9 years (Table II and Figure 3, B [available at www.jpeds.com]), and remained significant after 15 years of age.

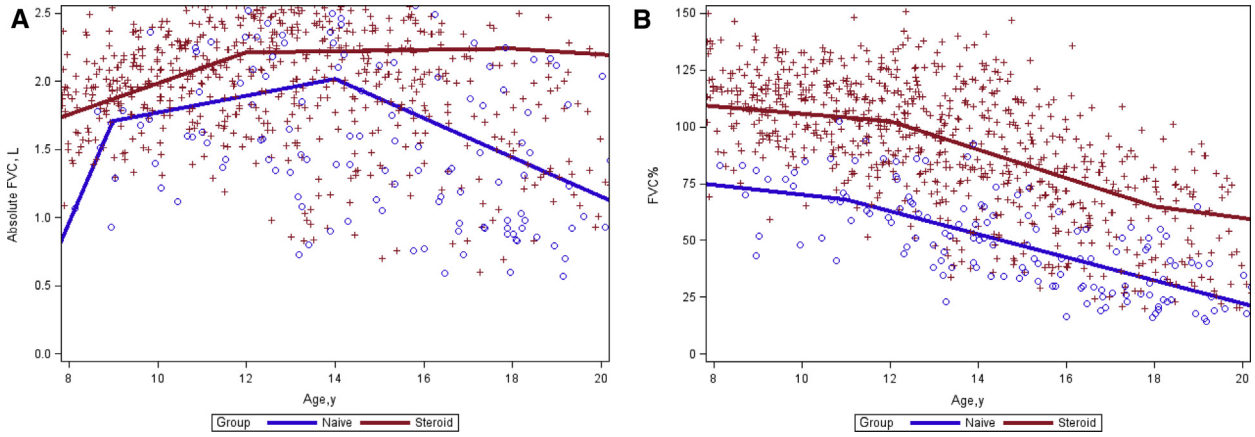

Figure 1. **A,** Regression model of absolute FVC (L) with age for glucocorticoid-treated (red) and glucocorticoid-naïve (blue) patients. Age on the *x*-axis was limited to 20 years for comparison between groups. **B,** Regression model of FVC% with age for glucocorticoid-treated (red) and glucocorticoid-naïve (blue) patients. Age on the *x*-axis was limited to 20 years for comparison between groups. At the age intervals of maximal FVC% decline, the glucocorticoid-treated (12-20 years) and the glucocorticoid-naïve (11-20 years) groups declined at similar rates (5.90 ± 0.26% vs 5.08 ± 0.39% per year; $P = .08$).

MIP% and MEP%

For the glucocorticoid-treated group, the rate of MIP% decline was most significant between the ages of 10 and 16 years (Table II). Similarly, the rate of MEP% decline in the glucocorticoid-treated group was most significant between 12 and 16 years of age (Table II).

Discussion

This study contrasts the rates of FVC decline in 2 large single-center cohorts of glucocorticoid-treated and glucocorticoid-naïve patients with DMD. The glucocorticoid-treated patients achieved significantly higher peak FVC values and at earlier ages than their glucocorticoid-naïve peers. The groups experienced similar plateau durations for absolute FVC, with the glucocorticoid-naïve group entering and exiting this plateau phase about 3 years before the glucocorticoid-treated group. The steepest FVC% declines in both groups began at about 11 and 12 years of age for the glucocorticoid-naïve and glucocorticoid-treated groups, respectively, with both groups declining at similar rates. A unique assessment of FVC% data across sequential ages allowed for the placing of individual glucocorticoid-treated patients in their respective deciles of FVC% (Figure 2), showing that these patients entered the phase of accelerated pulmonary decline at different ages. These data also show that patients at any given age may exhibit a wide range of FVC% values. Patients with lower FVC% seemed to enter the phase of accelerated FVC% decline earlier than those with higher function. It is, therefore, conceivable that patients may exhibit different responses in a given clinical trial based on their decile at inclusion into the trial. For example, two 11-year-old boys at the 10th and 60th deciles of FVC% may experience different degrees of decline over a year (Table IV). In addition, these data support the understanding that preservation of FVC% for longer durations of time represents crossing into higher decile ranges. The preservation of FVC% should thus be considered a valid and important endpoint in clinical trials. Related to this, the information from this study may allow for subject recruitment based on FVC% decile and neuromuscular function, as opposed to the more conventionally used ranges of age and lung function.

Mayer et al showed linear FVC% decline, and indicated that FVC% of ambulatory patients with DMD declined at the same rate once they became nonambulatory.[18] In another study, patients with DMD who reached Brooke's upper extremity score of 5 exhibited a marked decrease in pulmonary

Table IV. Deciles of FVC% for glucocorticoid-treated DMD patients

	Deciles of FVC%								
Ages, y	10	20	30	40	50	60	70	80	90
6	96.0	104.1	109.5	113.7	117.5	121.2	124.9	129.0	134.6
7	96.2	103.6	108.6	112.7	116.3	119.8	123.4	127.5	132.9
8	95.1	102.2	107.0	111.0	114.6	118.0	121.6	125.7	131.2
9	92.4	99.6	104.5	108.6	112.4	116.0	119.8	124.1	129.9
10	87.6	95.4	100.9	105.5	109.8	113.9	118.3	123.2	129.9
11	81.0	89.9	96.3	101.7	106.6	111.5	116.7	122.6	130.5
12	73.5	83.5	90.7	96.9	102.6	108.3	114.3	121.2	130.4
13	65.5	76.4	84.3	91.1	97.4	103.7	110.4	118.1	128.4
14	57.4	68.7	77.0	84.2	90.9	97.7	104.8	113.1	124.1
15	49.4	60.7	69.1	76.4	83.3	90.2	97.6	106.0	117.3
16	42.0	52.8	61.0	68.1	74.9	81.6	88.8	97.2	108.3
17	35.4	45.5	53.2	59.9	66.4	72.8	79.7	87.6	98.2
18	29.8	39.2	46.4	52.8	58.9	65.0	71.5	79.0	89.0
19	25.4	34.2	41.1	47.1	52.9	58.7	64.9	72.1	81.7
20	21.9	30.3	36.8	42.6	48.2	53.8	59.8	66.7	75.9
21	19.4	27.3	33.5	39.1	44.4	49.8	55.5	62.2	71.1
22	17.7	25.1	31.0	36.3	41.4	46.5	52.0	58.4	66.9
23	16.9	23.9	29.5	34.4	39.2	44.1	49.4	55.4	63.4
24	16.9	23.5	28.7	33.4	37.9	42.5	47.5	53.2	60.8

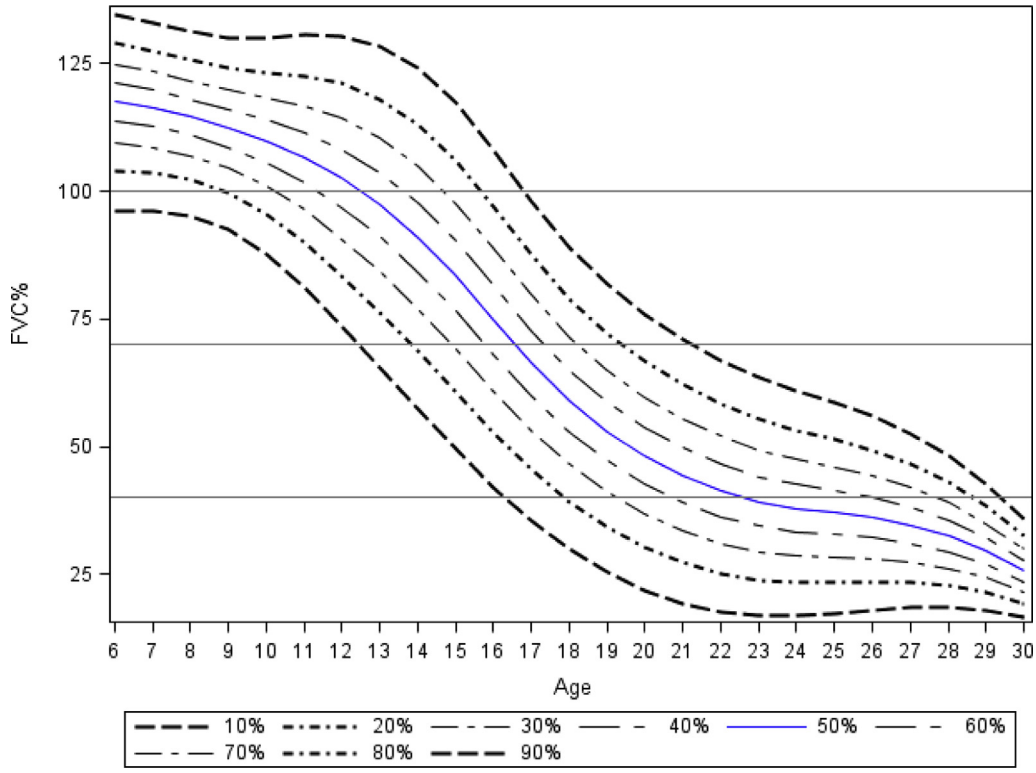

Figure 2. Deciles of FVC% in glucocorticoid-treated patients with DMD.

function, suggesting that pulmonary decline in DMD is not linear.[26] In keeping with previous findings,[18,27,28] we observed the absolute FVC increased early in the life of glucocorticoid-treated boys with DMD and stabilized through early adolescence, before declining in late adolescence. However, the FVC% trajectory in glucocorticoid-treated patients reflected 3 phases of decline: a slower rate of decline before 12 years and after 18 years of age, and an interval period of more rapid decline. During early adolescence, typically developing unaffected peers experience increases in height and lung capacities largely from their abilities to preserve vital capacity, by virtue of their physical activities (that serve to maintain composite respiratory compliance), and from the absence of chronic glucocorticoid treatment. However, glucocorticoid-treated patients with DMD lose ambulation in early adolescence. In the preceding years, these patients have already experienced prolonged periods of little or limited physical activity and fewer opportunities for activities that require deep breathing (such as running and jumping) that maintain respiratory compliance. As a result, there is progressive thoracic restriction with an early ceiling effect of absolute FVC. This finding explains the plateau of absolute FVC in the early teenage years of boys with DMD. The incorporation of various methods of lung volume augmentation may play a role in preserving respiratory compliance. The continued decline in FVC% can be explained by that fact that these values are compared with typically developing age-, height-, sex-, and race-matched unaffected peers who continue to grow and progress to puberty unimpeded. Aside from differences in muscle and lung function compared with their unaffected peers, boys with DMD experience glucocorticoid-induced growth failure and pubertal delay.[29-31] It should be noted that FVC% data may be influenced by glucocorticoid-induced growth failure and short stature, in addition to glucocorticoid-induced pubertal delay or hypogonadism, making interpretation more complex. The glucocorticoid-naïve patients revealed lower but stable absolute FVC values between the ages of 9 and 15 years, with gain and loss observed before and after this period, respectively. However, their yearly FVC% change revealed a slower rate of decline between the ages of 9 and 11 years, and a more rapid rate of decline thereafter. They achieved a lower ceiling of absolute FVC much earlier, before experiencing more rapid decline, when compared with their glucocorticoid-treated peers. Glucocorticoid therapy has been shown to delay these declines and improve lung function, although this effect seems to be short lived.[26] Our data support prior studies that showed similar rates of decline in glucocorticoid-naïve and glucocorticoid-treated patients.[18,32] From a clinical management perspective, the glucocorticoid-treated patients begin their decline from much higher levels of FVC% and at a later age, and are therefore unlikely to experience respiratory insufficiency until a later age.

The MIP% and MEP% revealed a consistent decline through the period of observation in glucocorticoid-treated patients, with an accelerated decline after the ages of 10 and 12 years. This accelerated decline precedes similar changes seen in FVC% and forced expiratory volume in 1 second

trajectories. It suggests that respiratory muscle weakness precedes the loss of lung volume. Similarly, the sniff inspiratory pressure was an earlier marker of decline in respiratory muscle strength than vital capacity in young glucocorticoid-naive patients with DMD.[33,34] In early adolescence, it is difficult to attribute the decline in vital capacity exclusively to a loss of respiratory muscle strength. Previous data have demonstrated that respiratory system compliance is reduced in general in patients with neuromuscular weakness.[35-38]

Previously, Humbertclaude et al demonstrated 3 distinct populations of glucocorticoid-naïve patients with DMD based on ages of loss of ambulation.[20] Correspondingly, the group that lost ambulation last experienced the lowest rates of pulmonary decline.[20] We have added to this concept by distributing FVC% data of glucocorticoid-treated boys with DMD across deciles to highlight variable ages of onset of accelerated FVC% decline. At any given age point, there is a spread of FVC% with different degrees of restriction. Conversely, it is possible to see patients of different ages at any given FVC%. This information is important in the context of therapeutic drug trial design in DMD and setting appropriate expectations of outcomes, because patients at different deciles will likely demonstrate variable responses to treatment. The concept of grouping together patients who have a similar natural history of pulmonary function over time (similar pulmonary phenotypes) via stratification based on the patients' ages at loss of ambulation could positively impact trial design. The long-term use of glucocorticoid therapy has been shown to preserve lung function over the first[19] and second decades of life,[39] thereby modifying the disease course. Our data demonstrate a similar effect of glucocorticoid therapy on FVC decline compared with glucocorticoid-naïve patients, although genotype and pulmonary phenotype variation between the 2 cohorts may exist that has not been accounted for.

A unique strength of the datasets from each of these 2 centers is that the patients had received longitudinal care exclusively at these respective centers, with consistent management recommendations and therapies for the duration of follow-up. The PFT data acquisition and interpretation were all performed by consistent technicians and physicians, and only those PFT data that met the rather strict ATS/ERS criteria were accepted for analysis. All these features make these clinical data of the highest possible quality. However, this study, being retrospective, carries some limitations. Over the period of observation, additional methods of height measurement were needed to accommodate for challenges posed by loss of ambulation or the ability to stand in older boys. Ulna length and arm span measures may influence height estimates, in the expected direction of overestimation of height, which may result in a reduction of FVC%, amplifying the observed pulmonary decline. Despite this being an inherent and inevitable caveat of using FVC% in this patient population that is important to recognize when interpreting their PFTs, any bias is likely to be similar between centers, and we believe that our data remain relevant and applicable in this setting. The use of current ATS criteria to include neuromuscular patient data carries the risk of excluding large amounts of data owing to the strict criteria that must be achieved, especially data of weaker and older patients in whom PFTs are challenging to perform. These tests are all effort dependent, and historic data suggest a great deal of interpatient and intrapatient variability.[33] It is possible that some patients contributed fewer or more data points than others, and this could lead to error. In this study, we have not defined the decline in PFTs in relation to the loss of other functions such as ambulation or upper extremity functions. These factors would be of clinical relevance as the patients continue to progress in their late second and third decades of life. Separate assessments of patients who underwent spine stabilization surgery were not performed because there were only a few patients in each group who underwent this procedure. The deciles were generated using a single cohort of patients followed at 1 center and highlight phenotypic variability. We acknowledge that a larger study would be needed to develop this further for broader application. Last, we did not include analyses related to patient genotype, or the type, dose, and duration of glucocorticoid exposure, although all glucocorticoid-treated patients were on similar standard dose daily therapy regimens. The degree of individual glucocorticoid responsiveness was not assessed.

We have shown that glucocorticoid-treated boys with DMD achieve significantly higher and normal levels of FVC, and achieve these peaks at younger ages than their glucocorticoid-naïve peers. Furthermore, their FVC% decline begins about 3 years after glucocorticoid-naïve patients' FVC% begins to decline. This decline is accelerated during adolescence in both groups, a time when growth discrepancies between patients and their unaffected peers are more pronounced, and when height measurements become more challenging. The declines in respiratory muscle strength in the glucocorticoid-treated patients precede FVC decline. The patients at the US center are evaluated and cared for in an interdisciplinary manner,[15] and the deciles of FVC% trajectories presented are an aggregate result of the comprehensive and integrated efforts of all disciplines, including neurology, cardiology, pulmonology, endocrinology, physiatry, and orthopedic teams, along with the services of physical therapists and nutritionists. Although these data are unique to this population, it is conceivable that the use of FVC% deciles in trial design in the era of glucocorticoid treatment would be useful, because there is clear evidence of glucocorticoid-treated patients experiencing accelerated pulmonary decline at different ages. We believe these data will allow for their improved stratification by FVC%, and perhaps more accurate inclusion criteria of patients into clinical studies. Alternate criteria for the assessment of pulmonary function in children with DMD have been suggested,[18] but are not yet widely used. Such criteria could also allow for expanded recruitment into clinical trials. ■

Submitted for publication Oct 10, 2018; last revision received Feb 7, 2019; accepted Feb 26, 2019.

Reprint requests: Hemant Sawnani, MD, Division of Pulmonary Medicine, MLC 7041, Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: Hemant.Sawnani@cchmc.org

References

1. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell 1987;51:919-28.
2. Hoffman EP, Fischbeck KH, Brown RH, Johnson M, Medori R, Loike JD, et al. Characterization of dystrophin in muscle-biopsy specimens from patients with Duchenne's or Becker's muscular dystrophy. N Engl J Med 1988;318:1363-8.
3. McDonald CM, Abresch RT, Carter GT, Fowler WM Jr, Johnson ER, Kilmer DD, et al. Profiles of neuromuscular diseases. Duchenne muscular dystrophy. Am J Phys Med Rehab 1995;74:S70-92.
4. Birnkrant DJ, Ararat E, Mhanna MJ. Cardiac phenotype determines survival in Duchenne muscular dystrophy. Pediatr Pulmonol 2016;51:70-6.
5. Rall S, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myol 2012;31:117-20.
6. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Dis 2002;12:926-9.
7. Drachman DB, Toyka KV, Myer E. Prednisone in Duchenne muscular dystrophy. Lancet 1974;2:1409-12.
8. Mendell JR, Moxley RT, Griggs RC, Brooke MH, Fenichel GM, Miller JP, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med 1989;320:1592-7.
9. Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT 3rd, Griggs RC, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. Neurology 1991;41:1874-7.
10. Fenichel GM, Mendell JR, Moxley RT III, Griggs RC, Brooke MH, Miller JP, et al. A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. Arch Neurol 1991;48:575-9.
11. Griggs RC, Moxley RT III, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol 1991;48:383-8.
12. Connolly AM, Schierbecker J, Renna R, Florence J. High dose weekly oral prednisone improves strength in boys with Duchenne muscular dystrophy. Neuromuscul Disord 2002;12:917-25.
13. Escolar DM, Hache LP, Clemens PR, Cnaan A, McDonald CM, Viswanathan V, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology 2011;77:444-52.
14. Schram G, Fournier A, Leduc H, Dahdah N, Therien J, Vanasse M, et al. All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 2013;61:948-54.
15. Wong BL, Rybalsky I, Shellenbarger KC, Tian C, McMahon MA, Rutter MM, et al. Long-term outcome of interdisciplinary management of patients with Duchenne muscular dystrophy receiving daily glucocorticoid treatment. J Pediatr 2017;182:296-303.e1.
16. Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. Pediatr Pulmonol 2008;43:1020-4.
17. Finder J, Mayer OH, Sheehan D, Sawnani H, Abresch RT, Benditt J, et al. Pulmonary endpoints in Duchenne muscular dystrophy: a workshop summary. Am J Respir Crit Care Med 2017;196:512-9.
18. Mayer OH, Finkel RS, Rummey C, Benton MJ, Glanzman AM, Flickinger J, et al. Characterization of pulmonary function in Duchenne muscular dystrophy. Pediatr Pulmonol 2015;50:487-94.
19. McDonald CM, Gordish-Dressman H, Henricson EK, Duong T, Joyce NC, Jhawar S, et al. Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: long-term natural history with and without glucocorticoids. Neuromuscul Disord 2018;28:897-909.
20. Humbertclaude V, Hamroun D, Bezzou K, Berard C, Boespflug-Tanguy O, Bommelaer C, et al. Motor and respiratory heterogeneity in Duchenne patients: implication for clinical trials. Eur J Paediatr Neurol 2012;16:149-60.
21. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
22. Miller F, Koreska J. Height measurement of patients with neuromuscular disease and contractures. Dev Med Child Neurol 1992;34:55-60.
23. Torres LA, Martinez FE, Manco JC. Correlation between standing height, sitting height, and arm span as an index of pulmonary function in 6-10-year-old children. Pediatr Pulmonol 2003;36:202-8.
24. Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol 2004;46:475-80.
25. Wan X, Qu Y, Huang Y, Zhang X, Song H, Jiang H. Nonparametric estimation of age-specific reference percentile curves with radial smoothing. Contemp Clin Trials 2012;33:13-22.
26. Meier T, Rummey C, Leinonen M, Spagnolo P, Mayer OH, Buyse GM, et al. Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy. Neuromuscul Disord 2017;27:307-14.
27. Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. J Pediatr 2001;138:45-50.
28. Rideau Y, Jankowski LW, Grellet J. Respiratory function in the muscular dystrophies. Muscle Nerve 1981;4:155-64.
29. Dooley JM, Bobbitt SA, Cummings EA. The impact of deflazacort on puberty in Duchenne muscular dystrophy. Pediatr Neurol 2013;49:292-3.
30. Lamb MM, West NA, Ouyang L, Yang M, Weitzenkamp D, James K, et al. Corticosteroid treatment and growth patterns in ambulatory males with Duchenne muscular dystrophy. J Pediatr 2016;173:207-13.e3.
31. Weber DR, Hadjiyannakis S, McMillan HJ, Noritz G, Ward LM. Obesity and endocrine management of the patient with Duchenne muscular dystrophy. Pediatrics 2018;142:S43-52.
32. Connolly AM, Malkus EC, Mendell JR. Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy. Muscle Nerve 2015;51:522-32.
33. Neve V, Cuisset JM, Edme JL, Carpentier A, Howsam M, Leclerc O, et al. Sniff nasal inspiratory pressure in the longitudinal assessment of young Duchenne muscular dystrophy children. Eur Respir J 2013;42:671-80.
34. Khirani S, Ramirez A, Aubertin G, Boule M, Chemouny C, Forin V, et al. Respiratory muscle decline in Duchenne muscular dystrophy. Pediatr Pulmonol 2014;49:473-81.
35. De Troyer A, Heilporn A. Respiratory mechanics in quadriplegia. The respiratory function of the intercostal muscles. Am Rev Respir Dis 1980;122:591-600.
36. Estenne M, De Troyer A. The effects of tetraplegia on chest wall statics. Am Rev Respir Dis 1986;134:121-4.
37. Estenne M, Gevenois PA, Kinnear W, Soudon P, Heilporn A, De Troyer A. Lung volume restriction in patients with chronic respiratory muscle weakness: the role of microatelectasis. Thorax 1993;48:698-701.
38. Estenne M, Heilporn A, Delhez L, Yernault JC, De Troyer A. Chest wall stiffness in patients with chronic respiratory muscle weakness. Am Rev Respir Dis 1983;128:1002-7.
39. Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, et al. The 6-minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr 2013;5.

Table I. Demographics of included patients

Subjects	Glucocorticoid naïve	Glucocorticoid treated	Past glucocorticoid treated
N	9* + 41†	170	5
No. of observations			
US population	59	847	15
French population	101	—	—
Steroid use			
Age start (y)	—	6.7 ± 2.3	10.4 ± 3.6
Duration of use (y)	—	8.3 ± 3.7	2.8 ± 1.5
Race			
Asian	3	5	—
Black	—	4	—
Other	1	2	1
White	46	159	4

Values are number or mean ± SD.
*Naive patients include 9 US and 41.
†French patients.

Table III. Peak FVC data for naïve and glucocorticoid-treated DMD patients

Measures	Glucocorticoid treated	Glucocorticoid naïve	*P* value
Age at peak absolute FVC, y	13.5 ± 3.0	14.3 ± 2.8	.03
Absolute FVC peak, L	2.4 ± 0.6	1.9 ± 0.7	<.0001
Age at peak FVC%, y	11.9 ± 2.9	13.6 ± 3.2	.002
FVC% peak	105 ± 25.1	56.0 ± 20.9	<.0001

Values are mean ± SD.

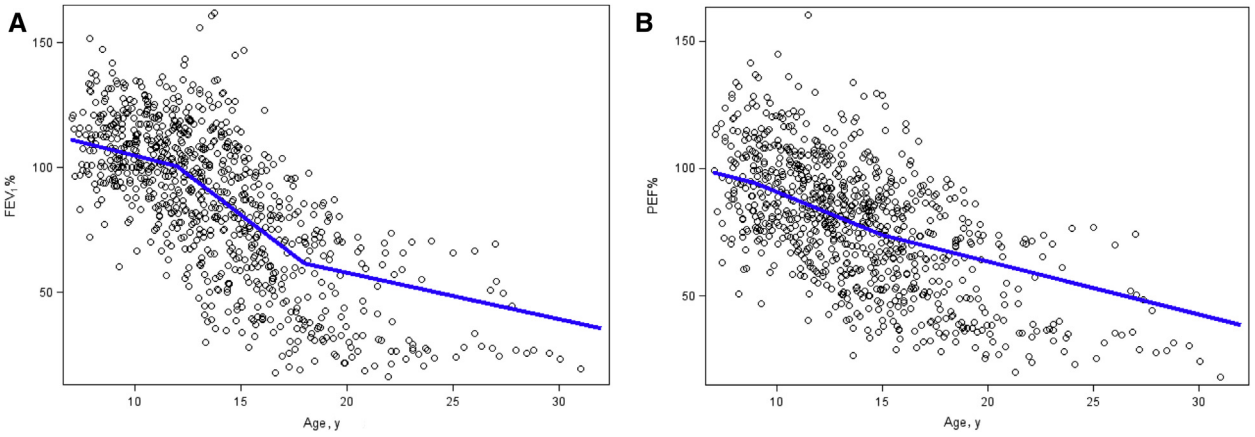

Figure 3. **A,** Regression model of forced expiratory volume in 1 second (FEV_1%) with age for glucocorticoid-treated patients. **B,** Regression model of peak expiratory flow rate (PEF%) with age for glucocorticoid-treated patients.