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All-Cause Mortality and Cardiovascular Outcomes With Prophylactic Steroid Therapy in Duchenne Muscular Dystrophy

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Objectives This study sought to determine the impact of steroid therapy on cardiomyopathy and mortality in patients with Duchenne muscular dystrophy (DMD).

Background DMD is a debilitating X-linked disease that afflicts as many as 1 in 3,500 boys. Although steroids slow musculoskeletal impairment, the effects on cardiac function and mortality remain unknown.

Methods We conducted a cohort study on patients with DMD treated with renin-angiotensin-aldosterone system antagonists with or without steroid therapy.

Results Eighty-six patients, 9.1 ± 3.5 years of age, were followed for 11.3 ± 4.1 years. Seven of 63 patients (11%) receiving steroid therapy died compared with 10 of 23 (43%) not receiving steroid therapy ($p = 0.0010$). Overall survival rates at 5, 10, and 15 years of follow-up were 100%, 98.0%, and 78.6%, respectively, for patients receiving steroid therapy versus 100%, 72.1%, and 27.9%, respectively, for patients not receiving steroid therapy (log-rank $p = 0.0005$). In multivariate propensity-adjusted analyses, steroid use was associated with a 76% lower mortality rate (hazard ratio: 0.24; 95% confidence interval: 0.07 to 0.91; $p = 0.0351$). The mortality reduction was driven by fewer heart failure–related deaths (0% vs. 22%, $p = 0.0010$). In multivariate analyses, steroids were associated with a 62% lower rate of new-onset cardiomyopathy (hazard ratio: 0.38; 95% confidence interval: 0.16 to 0.90; $p = 0.0270$). Annual rates of decline in left ventricular ejection fraction (−0.43% vs. −1.09%, $p = 0.0101$) and shortening fraction (−0.32% vs. −0.65%, $p = 0.0025$) were less steep in steroid-treated patients. Consistently, the increase in left ventricular end-diastolic dimension was of lesser magnitude (+0.47 vs. +0.92 mm per year, $p = 0.0105$).

Conclusions In patients with DMD, steroid therapy is associated with a substantial reduction in all-cause mortality and new-onset and progressive cardiomyopathy. (J Am Coll Cardiol 2013;61:948–54) © 2013 by the American College of Cardiology Foundation

Duchenne muscular dystrophy (DMD) is an X-linked, recessively inherited, debilitating degenerative disease with an estimated incidence ranging from 1 in 3,500 to 6,000 live male births (1–3). The life expectancy averages between 19 and 25 years and is limited by cardiorespiratory complications (1,4,5). Lack of dystrophin, a protein that connects the cytoskeleton to the external basement membrane, promotes myocyte necrosis and subsequent fibrosis (6,7), which may lead to progressive left ventricular dilation and failure (8–10). Cardiomyopathy is associated with a poor prognosis (11–13) and accounts for 20% to 40% of all deaths (14–16). Therapeutic studies aimed at halting the progression of left ventricular dysfunction have largely focused on antagonists of the renin-angiotensin-aldosterone system (11,17,18). Steroid treatment with prednisone or deflazacort has been associated with prolongation of ambulation and improved forced vital capacity (19,20). However, the effect of steroid therapy on the prevention and progression of cardiomyopathy has not been fully explored. Moreover, it has yet to be determined whether steroids improve overall survival. We, therefore, sought to assess the impact of steroid therapy on all-cause mortality and new-onset and progressive left ventricular dysfunction in a cohort of patients with DMD.

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Methods

Study population. A retrospective cohort study was conducted on patients with DMD born between January 1, 1972, and December 31, 2006, and followed at the Neuromuscular Clinic of the Marie-Enfant Rehabilitation Center, Université de Montréal. To qualify for inclusion, patients were required to have a confirmed diagnosis of DMD on the basis of gene deletion or the absence of dystrophin on biopsy.

The study was approved by the local institutional review board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Pharmacological therapy. All patients received antagonists of the renin-angiotensin-aldosterone system, with an angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker. Steroid therapy was at the discretion of caregivers, the patient, and his family after candid discussions regarding potential benefits (e.g., preservation of muscle and respiratory function), variable responses, side effects, and uncertainties in the absence of long-term controlled trials. Prescribed steroids consisted of deflazacort at a dose of 0.9 mg/kg/day or prednisone at a dose ranging from 0.5 to 0.75 mg/kg/day. At the time of steroid initiation, elementary calcium (250 mg 3 times a day) and vitamin D (400 IU daily) were administered to all patients.

Follow-up. Routine cardiology follow-up was scheduled every 6 months. At each follow-up visit, blood pressure, weight, and height were recorded. To screen for conduction system abnormalities or arrhythmia, electrocardiograms were obtained at every visit. The PR interval, QRS duration, corrected QT interval, and heart rate were logged. The primary outcome consisted of all-cause mortality. Original source material was reviewed for all fatalities. Death was considered secondary to heart failure if it complicated worsening heart failure, as defined by evidence of at least 1 of the following: orthopnea, nocturnal dyspnea, pulmonary edema, increasing peripheral edema, renal hypoperfusion (i.e., worsening renal function), or radiological signs of congestive heart failure (21).

Serial transthoracic echocardiograms were obtained every 6 to 12 months to assess left ventricular size and function. Left ventricular internal dimensions in end-systole and end-diastole were determined in parasternal long-axis views. *z*-Scores were expressed using the Haycock formula to calculate body surface area (22). Estimates of left ventricular ejection fractions were based on the Teichholz method of quantification (23). Left ventricular function was classified as normal, mildly impaired, moderately impaired, or severely impaired if the ejection fraction was ≥55%, 45% to 54%, 30% to 44%, and <30%, respectively, in accordance with recommendations from the American Society of Echocardiography (23). Cardiomyopathy was also dichotomously defined as present or absent according to whether left ventricular function was at least moderately impaired (i.e., ejection fraction <45% vs. ≥45%). The left ventricular endocardial shortening fraction was calculated using minor-axis internal diameters obtained from a standard M-mode tracing with the following equation: shortening fraction = (end-diastolic dimension − end-systolic dimension) ÷ end-diastolic dimension. As per guidelines, the shortening fraction was considered normal, mildly abnormal, moderately abnormal, or severely abnormal for values ≥25%, 20% to 24%, 15% to 19%, and <15%, respectively (23).

Abbreviation and Acronym

DMD = Duchenne muscular dystrophy

Data analysis. Continuous variables are presented as mean ± SD or median and interquartile range (25th, 75th percentile), depending on their distribution. Categorical variables are summarized by frequencies and percentages. Comparisons between patients who did and did not receive steroids were performed using chi-square tests, Student *t* tests, or Mann-Whitney rank sum tests, where appropriate. The Fisher exact test was used for categorical variables with cell counts <5. Event-free survival curves for all-cause mortality and freedom from new-onset cardiomyopathy were estimated by the Kaplan-Meier method and compared using the log-rank test. A propensity score was generated by multivariate logistic regression with steroid therapy modeled as the outcome variable and the following covariates: age at initial cardiac evaluation, left ventricular ejection fraction, left ventricular shortening fraction, left ventricular end-diastolic dimension and its *z*-score, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, beta-blocker, digoxin, and diuretic agents. After verifying proportionality assumptions, factors associated with a p value <0.2 in univariate Cox regression analyses were considered in multivariate stepwise Cox regression models that included steroid use as the main independent variable and adjusted for the propensity score.

Given that severity of cardiomyopathy is an ordinal outcome variable (i.e., absent, mild, moderate, severe), longitudinal generalized estimating equation analysis was performed using the multinomial distribution with steroids, time, and their interaction term (i.e., steroids × time) as main independent variables. A significant interaction was considered indicative of a differing average slope between patients receiving and not receiving steroid therapy. In this model, time was treated as a continuous variable. Potential predictors were included in the generalized estimating equation model using a backward selection procedure. Analyses of serial echocardiographic and electrocardiographic parameters were similarly performed using a longitudinal generalized estimating equation approach. Two-tailed p values <0.05 were considered statistically significant. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Study population. During the study period, 86 patients diagnosed with DMD met inclusion criteria, 63 (73%) of whom were prescribed steroids. Baseline characteristics

Table 1 Baseline Characteristics

	All Patients (N = 86)	Steroid Therapy (n = 63)	No Steroid Therapy (n = 23)	p Value
Age at initial cardiac evaluation, yrs	9.1 ± 3.5	8.5 ± 2.9	10.8 ± 4.3	0.0267
Age at initiation of RAASa, yrs	12.9 ± 4.3	12.0 ± 3.4	15.1 ± 5.5	0.0162
ACE inhibitor	74 (86)	54 (86)	20 (87)	0.8830
Angiotensin receptor blocker	35 (41)	28 (44)	7 (30)	0.2418
ACE inhibitor and ARB	23 (27)	19 (30)	4 (17)	0.2364
Beta-blockers	53 (62)	41 (65)	12 (52)	0.2160
Digoxin	22 (26)	12 (19)	10 (43)	0.0215
Diuretic agents	8 (9)	3 (5)	5 (22)	0.0164
LV ejection fraction, %	58 ± 6	59 ± 5	56 ± 8	0.1704
Normal	61 (76)	47 (77)	14 (73)	
Mildly impaired	17 (21)	14 (23)	3 (16)	
Moderately impaired	2 (3)	0 (0)	2 (11)	
Severely impaired	0 (0)	0 (0)	0 (0)	
LV shortening fraction, %	32 ± 4	32 ± 3	30 ± 5	0.1486
Normal	78 (98)	61 (100)	17 (90)	
Mildly abnormal	1 (1)	0 (0)	1 (5)	
Moderately abnormal	1 (1)	0 (0)	1 (5)	
Severely abnormal	0 (0)	0 (0)	0 (0)	
LV end-diastolic dimension, mm	41 ± 5	40 ± 3	43 ± 7	0.0956
z-score LV end-diastolic dimension	0.89 ± 1.11	0.91 ± 1.04	0.80 ± 1.34	0.7220
LV end-systolic dimension, mm	28 ± 5	27 ± 3	30 ± 8	0.1471
PR interval, ms*	116 (108, 120)	115 (108, 120)	120 (114, 120)	0.3716
QRS duration, ms*	80 (80, 88)	80 (80, 88)	80 (70, 80)	0.1537
Corrected QT interval, ms*	404 (400, 416)	404 (400, 418)	404 (390, 410)	0.5112

Values are mean ± SD or n (%). *Non-normally distributed continuous variables are summarized by median and interquartile range (25th, 75th percentile).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LV = left ventricular; RAASa = renin-angiotensin-aldosterone system antagonist.

are summarized in Table 1. Patients receiving steroid therapy were assessed by cardiology and prescribed a renin-angiotensin-aldosterone system antagonist at a younger age. Steroid therapy was initiated at a mean age of 8.6 ± 3.5 years. Patients receiving steroid therapy were less likely to receive digoxin and a diuretic agent, but not a beta-blocker. No statistically significant differences in echocardiographic or electrocardiographic parameters were observed between the 2 groups at baseline.

Mortality. A total of 17 patients (20%) died over the course of follow-up, which averaged 11.3 ± 3.6 years versus 11.3 ± 5.1 years in patients receiving and not receiving steroid therapy, respectively (p = 0.9671). Seven of the 63 patients (11%) receiving steroid therapy died compared with 10 of 23 patients (43%) not receiving steroid therapy (p = 0.0010). Freedom from all-cause mortality is depicted in Figure 1. Overall survival rates at 5, 10, and 15 years of follow-up were 100%, 98.0%, and 78.6%, respectively, for patients receiving steroid therapy versus 100%, 72.1%, and 27.9%, respectively, for patients not receiving steroid therapy (log-rank p = 0.0005). Univariate and propensity-adjusted multivariate predictors of all-cause mortality are summarized in Table 2. The only variables independently associated with all-cause mortality were steroid therapy (hazard ratio: 0.24; 95% confidence interval: 0.07 to 0.91; p = 0.0351) and a lower left ventricular ejection fraction (hazard ratio: 0.89 for a 1% unit change; 95% confidence interval: 0.82 to 0.96; p = 0.0023).

Causes of death in all patients and according to whether steroids were received are listed in Table 3. Steroids were

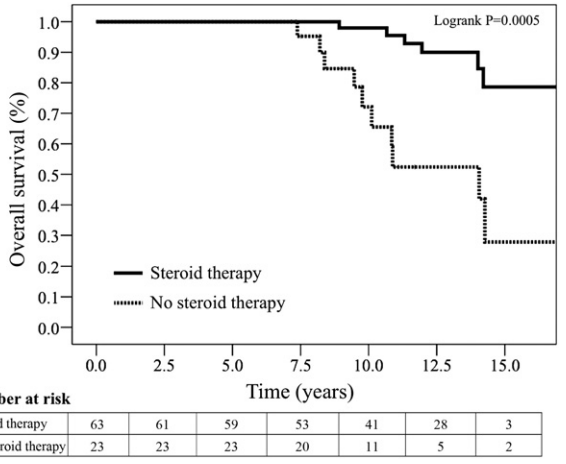

Figure 1 Overall Survival in Patients With and Without Steroids

Kaplan-Meier curves depict freedom from all-cause death in patients with Duchenne muscular dystrophy who did and did not receive steroid therapy.

Table 2 Factors Associated With All-Cause Mortality

	Hazard Ratio	95% Confidence Interval	p Value
Univariate analysis			
Steroid therapy	0.18	0.07, 0.50	0.0010
Age at initial cardiac evaluation per year	1.18	1.01, 1.38	0.0365
LV ejection fraction, per 1% change	0.85	0.80, 0.90	<0.0001
Digoxin therapy	2.17	0.82, 5.69	0.1171
Multivariate propensity-adjusted analysis			
Steroid therapy	0.24	0.07, 0.91	0.0351
LV ejection fraction, per 1% change	0.89	0.82, 0.96	0.0023

LV = left ventricular.

associated with significantly fewer heart failure–related deaths (0% vs. 22%, p = 0.0010). The number of deaths due to respiratory failure and other causes was not significantly different between the 2 groups.

Clinical follow-up. Patients receiving steroid therapy were treated for an average of 11.0 ± 4.8 years. Characteristics at the last follow-up visit are summarized in Table 4. Despite a nonsignificant difference in age, patients receiving steroid therapy were substantially shorter than those not receiving steroid therapy (149 ± 14 cm vs. 167 ± 11 cm, p < 0.0001), yielding a significantly lower body mass index (19 ± 7 kg/m^2 vs. 24 ± 6 kg/m^2, p = 0.0017). Steroid therapy was not associated with a difference in weight, blood pressure, or heart rate.

Cardiac parameters. Cardiomyopathy developed in a total of 21 (28%) patients (i.e., 7 of 63 patients (11%) receiving steroid therapy and 14 of 23 patients (61%) not receiving steroid therapy (p < 0.0001). Freedom from new-onset cardiomyopathy in patients receiving and not receiving steroid therapy is shown in Figure 2. Freedom from cardiomyopathy at 5, 10, and 15 years of follow-up was 96.8%, 94.4%, and 84.1%, respectively, for patients receiving steroid therapy versus 95.2%, 73.9%, and 29.6%, respectively, for patients not receiving steroid therapy (log-rank p < 0.0001). Univariate and propensity-adjusted multivariate predictors of new-onset cardiomyopathy are listed in Table 5. Steroid therapy was the only variable independently associated with cardiomyopathy (hazard ratio: 0.38; 95% confidence interval: 0.16 to 0.90; p = 0.0270).

The decline in left ventricular ejection fraction over time was significantly less steep in patients who did versus those who did not receive steroid therapy (annual rate of change: −0.43% vs. −1.09%, p = 0.0101). Similarly, the annual reduction in fractional shortening was significantly less in steroid-treated patients (−0.32% vs. −0.65%, p = 0.0025). Consistently, the annual increase in left ventricular end-diastolic dimension was of lesser magnitude in patients who received steroid therapy compared with those who did not (+0.47 mm vs. +0.92 mm per year, p = 0.0105). Changes in electrocardiographic parameters (i.e., PR interval, QRS duration, and QTc interval) were similar in patients receiving and not receiving steroid therapy and were not associated with left ventricular dysfunction. No sustained atrial or ventricular tachyarrhythmia or a bradyarrhythmia requiring pacemaker implantation developed in any patients.

Discussion

DMD is a progressive disease with musculoskeletal symptoms that are usually clinically apparent before 4 years of age. The lack of dystrophin is associated with increased production of nitric oxide, which, along with abnormal calcium homeostasis and reactive oxygen species, has been implicated in the genesis of fibrosis (24–26). Although cardiomyopathy is rarely diagnosed before 10 years of age (27), a lengthy subclinical phase may presage symptom onset (28–31). Cardiac fibrosis characteristically begins in the posterobasal segment of the left ventricle (16) and may spread throughout the myocardium (8–10). Increased wall stress and afterload may contribute to progressive left ventricular dilation and, ultimately, dysfunction (32). Therapeutic studies, largely observational in nature, suggest that

Table 3 Causes of Death

	All Patients (N = 86)	Steroid Therapy (n = 63)	No Steroid Therapy (n = 23)	p Value
Heart failure	5 (6)	0 (0)	5 (22)	0.0010
Respiratory failure	9 (10)	5 (8)	4 (17)	0.2402
Other	3 (3)	2 (3)	1 (4)	1.0000
Pulmonary embolism	1 (1)	1 (2)	0 (0)	
Testicular cancer	1 (1)	1 (2)	0 (0)	
Unknown	1 (1)	0 (0)	1 (4)	
All-cause mortality	17 (20)	7 (11)	10 (43)	0.0010

Values shown are n (%).

Table 4 Patient Characteristics at Last Follow-Up

	All Patients (N = 86)	Steroid Therapy (n = 63)	No Steroid Therapy (n = 23)	p Value
Age at last follow-up, yrs	20.4 ± 5.7	19.8 ± 5.5	22.1 ± 5.8	0.0910
Height, cm	153 ± 15	149 ± 14	167 ± 11	<0.0001
Weight, kg	54 ± 18	54 ± 16	54 ± 24	0.9284
Body mass index, kg/m^2	23 ± 7	24 ± 6	19 ± 7	0.0017
Systolic blood pressure, mm Hg	104 ± 14	104 ± 14	102 ± 13	0.5509
Diastolic blood pressure, mm Hg	67 ± 11	67 ± 11	66 ± 11	0.5404
Heart rate, beats/min	89 ± 17	89 ± 14	89 ± 22	0.9796
RAASa treatment duration, yrs	7.9 ± 3.2	8.1 ± 3.4	7.3 ± 2.9	0.2900
LV ejection fraction, %	50 ± 10	53 ± 7	42 ± 13	0.0008
Normal	30 (35)	27 (43)	3 (13)	
Mildly impaired	35 (41)	29 (46)	6 (26)	
Moderately impaired	15 (17)	6 (10)	9 (39)	
Severely impaired	6 (7)	1 (2)	5 (22)	
LV shortening fraction, %	27 ± 6	29 ± 5	23 ± 7	0.0043
Normal	67 (80)	56 (90)	11 (50)	
Mildly abnormal	8 (9)	2 (3)	6 (27)	
Moderately abnormal	5 (6)	3 (5)	2 (9)	
Severely abnormal	4 (5)	1 (2)	3 (14)	
LV end-diastolic dimension, mm	47 ± 8	46 ± 7	51 ± 11	0.0341
LV end-systolic dimension, mm	35 ± 9	32 ± 7	40 ± 12	0.0146
PR interval, ms*	120 (112, 134)	120 (112, 134)	120 (114, 124)	0.9565
QRS duration, ms*	90 (84, 100)	90 (84, 100)	90 (88, 100)	0.4966
Corrected QT interval, ms*	415 (401, 429)	420 (405, 429)	409 (392, 415)	0.1182
Follow-up duration, yrs	11.3 ± 4.0	11.3 ± 3.6	11.3 ± 5.1	0.9671

Values shown are mean ± SD or n (%). *Non-normally distributed continuous variables are summarized by median and interquartile range (25th, 75th percentile).
Abbreviations as in Table 1.

antagonists of the renin-angiotensin-aldosterone system alone, or in combination with a beta-blocker, delay the course of progressive left ventricular dysfunction (11,17,18).

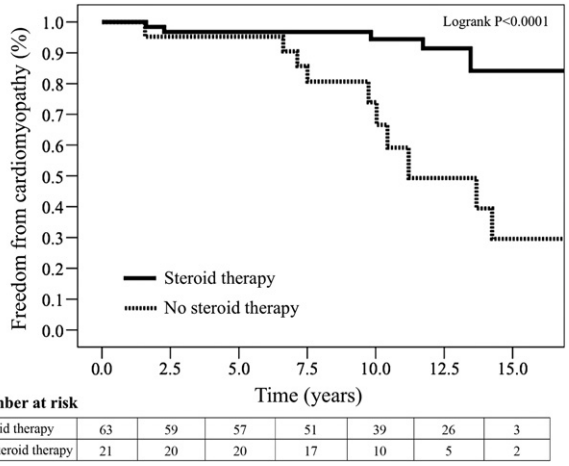

Figure 2 Freedom From Cardiomyopathy in Patients With and Without Steroid Therapy

The Kaplan-Meier curves plot freedom from new-onset cardiomyopathy, as defined by a left ventricular ejection fraction <45%, in patients with and without steroid therapy.

Corticosteroids (i.e., namely prednisone and deflazacort) are commonly used to treat musculoskeletal and respiratory complications in DMD, with no perceived differences in efficacy between the 2 agents (2,19,20,33). To our knowledge, our study is the first to explicitly assess the impact of steroids on all-cause mortality. In multivariate propensity-adjusted analyses that controlled for factors such as age, concomitant pharmacological therapy, echocardiographic parameters, and electrocardiographic metrics, steroid therapy was associated with a statistically significant 76% lower mortality rate. These findings are consistent with those of a previous study of 74 patients with DMD, 40 of whom were treated with deflazacort for an average of 5.5 years (2). Twelve of 34 boys (35%) who did not receive deflazacort died in their second decade of life compared with to 2 of 40 boys (5%) treated with deflazacort. A mortality analysis was not specifically performed, and concomitant medications were not reported.

The mortality reduction observed in our study appeared to be driven by significantly fewer heart failure–related deaths, as evidenced by the analysis of modes of death. Consistently, steroid therapy was associated with a 62% lower rate of new-onset cardiomyopathy, defined by a left ventricular ejection fraction <45%. This finding was independent of the left ventricular ejection fraction at baseline and other clinical, electrocardiographic, and echocardio-

Table 5 Factors Associated With New-Onset Cardiomyopathy

	Hazard Ratio	95% Confidence Interval	p Value
Univariate analysis			
Steroid therapy	0.20	0.07–0.52	0.0011
Beta-blocker therapy	0.31	0.08–1.17	0.0830
LV ejection fraction, per 1% change	0.93	0.90–0.96	<0.0001
Multivariate propensity-adjusted analysis			
Steroid therapy	0.38	0.16–0.90	0.0270
LV ejection fraction, per 1% change	0.96	0.93–1.01	0.0832

LV = left ventricular.

graphic parameters. Moreover, the rate of decline in left ventricular ejection fraction and fractional shortening was less steep in steroid-treated patients. Congruent with these findings, left ventricular dilation progressed at a slower rate.

Taken together, these results are consistent with and further extend the findings of previous small studies investigating the effect of corticosteroids on left ventricular function (2,19,33,34). In a retrospective analysis, 21 boys who received deflazacort had superior fractional shortening values and smaller left ventricular dimensions compared with 11 untreated patients (35). In another study that included 40 patients treated with deflazacort, the left ventricular ejection fraction decreased to <45% in 10% versus 58% of steroid- versus nonsteroid-treated patients at 5.5 years of follow-up, respectively (2). Markham et al. (33) similarly found that deflazacort or prednisone administered for 3.0 ± 2.5 years was associated with a greater fractional shortening. However, concomitant medical therapy was not reported. In a follow-up study of 14 treated and 23 untreated patients, the same authors noted that beneficial effects persisted after an average of 12 years (34). Houde et al. (19) likewise found that the left ventricular ejection fraction and fractional shortening were superior in 38 steroid-treated boys compared with 48 untreated patients with DMD. Steroid-treated patients were, however, far more likely to have received an antagonist of the renin-angiotensin-aldosterone system, obscuring the interpretation of these results.

Steroid therapy is not without drawbacks. For osteoporosis prevention, calcium and vitamin D supplements were administered to all patients receiving steroids. Although weight gain is common at the onset of therapy, no differences in weight were detected in steroid- versus nonsteroid-treated patients after an average follow-up of 11 years. Although hypertension is a well-recognized complication of steroid therapy, systolic and diastolic blood pressures were similar in patients with and without steroids. However, steroid-treated patients were of significantly shorter stature than nonsteroid-treated patients, likely reflecting long-term effects on growth suppression (19).

Study limitations. This study was nonrandomized and, as such, subject to the limitations inherent to observational studies. Although multivariate analyses adjusted for a propensity score along with clinical, pharmacological, echocardiographic, and electrocardiographic parameters, they cannot control for unknown or unmeasured potential confounders. Endpoint counts were small for multivariate modeling, and larger sample sizes in replication are needed. Nevertheless, given the very large magnitudes of effect, the study was adequately powered to detect differences in the primary (i.e., all-cause mortality) and all secondary endpoints (i.e., new-onset cardiomyopathy and progressive changes in left ventricular size and function). Moreover, the results were unchanged in analyses that excluded the 2 patients with moderately impaired left ventricular function at baseline. A randomized clinical trial would ideally be required to definitively establish a cause-and-effect relationship between steroids and improved outcomes.

Conclusions

In this observational study of patients with DMD, steroid therapy was associated with a considerably lower all-cause mortality rate, due largely to a significant reduction in heart failure–related deaths. Steroid-treated patients experienced a much lower incidence of new-onset cardiomyopathy. Moreover, left ventricular size and function were better preserved in patients receiving steroids. These provocative findings, which require confirmation from larger preferably randomized studies, offer new hope to patients with this progressive, incapacitating, and ultimately fatal form of muscular dystrophy.

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