The Natural History of Duchenne Muscular Dystrophy in the Corticosteroid Era: A Systematic Review of Studies from Canada and the US

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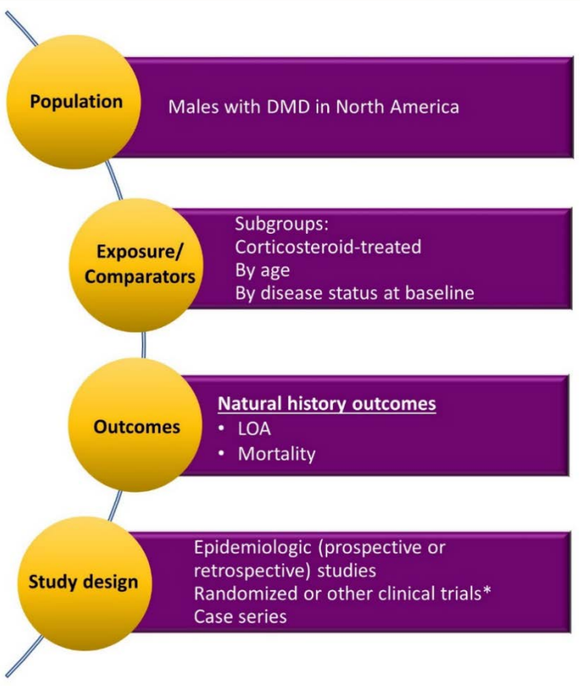
BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare severe progressive myopathy characterized by early loss of ambulation (LOA) and reduced life expectancy.
- While there is presently no cure, the use of corticosteroids since the 1990s have helped alleviate symptoms, manage complications and slow progression among patients with DMD.
- Data to characterize the natural history of DMD are limited, due to its rarity and challenges in following large cohorts over sufficiently long periods of time to observe key outcomes.
- The generalizability of older reviews on the natural history of DMD may be limited.
- Understanding the contemporary natural history of DMD patients treated with corticosteroids is important. No comprehensive reviews of the age at key natural history milestones, such as LOA and death, have been conducted.
- The objective of the present study was therefore to summarize estimates of age at LOA and death from studies of corticosteroid-treated patients with DMD in North America.

METHODS

- A systematic review was conducted using Medline/Medline in process and EMBASE for literature published in English between 1946 and November 2018.
- All abstracts were independently reviewed by two researchers against the Patient, Exposures/Comparators, Outcomes & Study (PECOS) criteria (**Figure 1**)
  - Studies with ≥50 corticosteroid-treated DMD patients from North America were included.
  - Samples were stratified by whether the entire cohort was corticosteroid-treated ('CS-treated'), or if the sample included a mix of corticosteroid-treated and -untreated patients ('Mixed').
    - If corticosteroid use was not described, but the study occurred after 1990, corticosteroid treatment was defined as 'Unknown'.
- Data from eligible studies were extracted in duplicate
  - Baseline demographics and clinical characteristics of samples included were tabulated
  - Outcomes of interest included:
    - Mean or median age at LOA and death
    - The percentage of the sample who experienced the outcome at time of reporting (where available)
- The strength of the available evidence was assessed using the STROBE Statement for observational studies and non-randomized clinical trials; and the Cochrane Risk of Bias tool for comparative studies (*data not shown*)

Figure 1. PECOS criteria



Abbreviations: DMD: Duchenne muscular dystrophy; LOA: Loss of ambulation

FUNDING & DISCLOSURES

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RESULTS

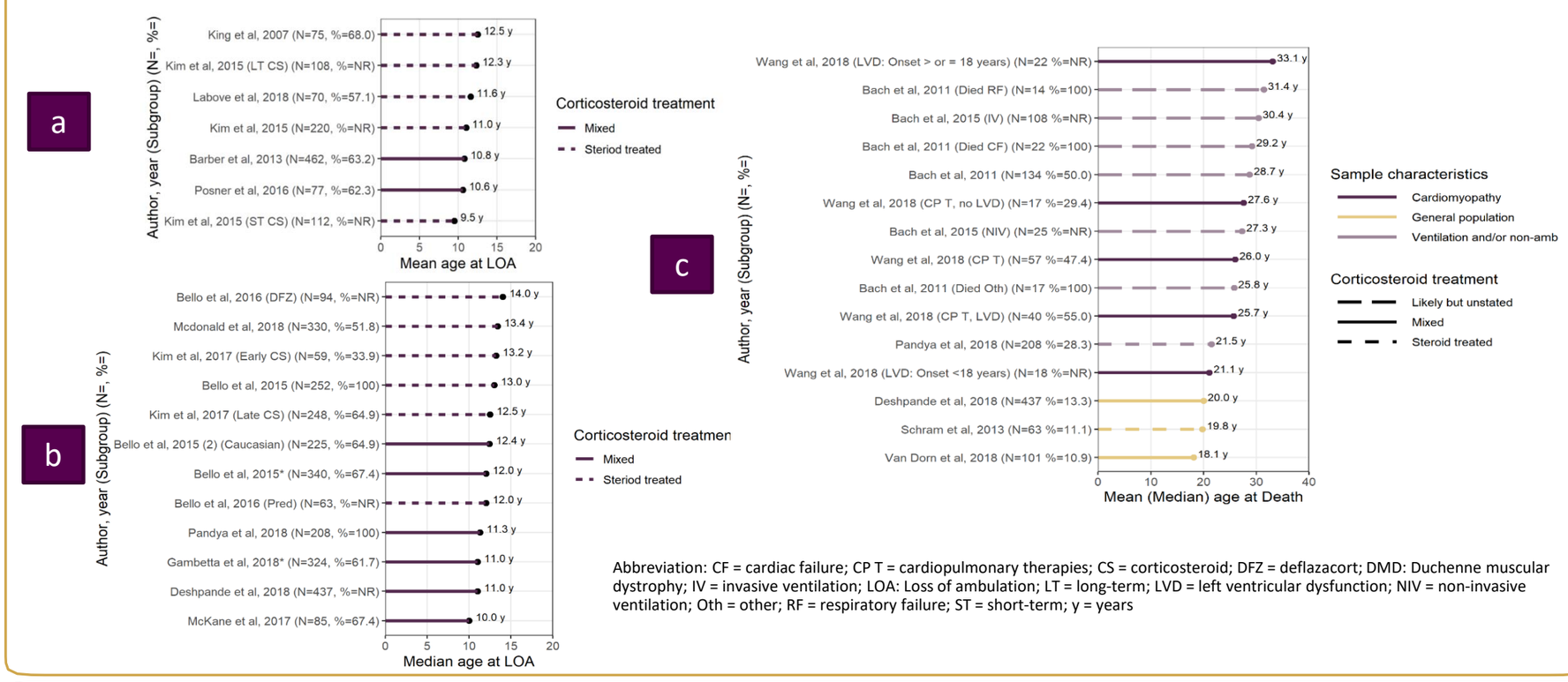
- Of 5,637 records identified, 14 studies reported age at LOA, and 7 age at death (two of which also reported age at LOA).
- Details on patient and study characteristics are presented in **Table 1.**
- Both prospective and retrospective studies were identified
- Types of corticosteroids used, dose, frequency, duration and age at initiation varied across the included studies (*additional details available from review authors*).
  - Nine studies reported details on the type of corticosteroid treatment received; all included patients treated with prednisone and deflazacort, and 4 also allowed included patients treated with prednisolone
- Estimates of mean age at LOA, reported in 5 studies, ranged from 9.5 (% with LOA not reported (NR) in n=112) among prednisone/deflazacort treated patients to 12.5 (LOA in 68% of n=75) years among prednisone/deflazacort treated patients (Figure 2a).
- Estimates of median age at LOA, reported in 10 studies, ranged from 10.0 (LOA in 67.4% of n=85) among mixed corticosteroid-treated patients to 14.0 (% with LOA NR in n=94) years among deflazacort treated patients (**Figure 2b**).
  - When mixed corticosteroid-treatment samples were excluded, the range was 12.0 (n=63) among prednisone treated patients to 14.0 (n=94) years (% with LOA NR)) among deflazacort treated patients.
- Mean age at death was reported in 6 studies
  - Mean age at death from 3 studies enrolling pediatric patients ranged from 18.1 (in 10.9% of n=101) among prednisone/deflazacort treated patients, to 20.0 (in 13.3% of n=437) years among a sample mixed corticosteroid patients (**Figure 2c**).
  - Mean age at death from 3 separate studies enrolling ventilated / non-ambulatory patients, ranged from 27.3 (n=25) to 30.4 (n=108) years (% deaths NR) among corticosteroid treated patients (unstated); and was 26.0 (47.4% of n=114) years in one study of mixed corticosteroid treated patients with cardiomyopathy (**Figure 2**c).

Table 1. Study and patient characteristics

Citation	n	Sample characteristics	Mean age at baseline, y	Study design/Data source	Follow-up, y
Bach, 2011+	134	Requiring ventilatory support	19.0	Single center chart review	Mean, 11.5
Bach, 2015+	133	Requiring ventilatory support	18.6	Single center chart review	Mean, 8.7 Max (29)
Barber, 2013*	462	Ambulatory DMD	7.4	MD STARnet	Mean, 4
Bello, 2015	252	Ambulatory DMD	6.8	CINRG-DNHS	Mean, 3.8
Bello, 2015 (2)*	225	Ambulatory DMD	NR	CINRG-DNHS	Mean, 4
Bello, 2016	157	Ambulatory DMD	NR	CINRG-DNHS	Mean, 4
Deshpande, 2018*	437	Ambulatory and non- ambulatory DMD	Unclear; study entry in 2005	Administrative	Unclear; 10 per patient
Gambetta, 2018*	324	Ambulatory and non-ambulatory DMD	6.0	Multicenter chart review	Unclear; 10 per patient
Kim, 2015	220	Ambulatory DMD	Unclear; CS started age 7	MD STARnet	Unclear; 29
Kim, 2017	307	Ambulatory DMD	2.6	MD STARnet	Median, 11-15
King, 2007	75	Ambulatory and non-ambulatory DMD	15.7	Single center chart review	Up to 3
Labove, 2018	70	Cannot climb stairs	CS started age 7	Single center chart review	Unclear; ≥7 per patient
Mcdonald, 2018	330	Ambulatory and non-ambulatory DMD	10.7	CINRG-DNHS	Unclear; >10 per patient
McKane, 2017*	85	Ambulatory and non-ambulatory DMD	14.9	Single center chart review	Unclear; >6 per patient
Pandya, 2018*	208	Adults (non-ambulatory) with DMD	Unstated; 'adults'	MD STARnet	Unclear; >10 per patient
Posner, 2016*	77	Ambulatory and non-ambulatory DMD	14.1	Single center chart review	Unclear; 18 per patient
Schram, 2013	63	Patients treated with cardioprotective meds	9.1	Single center chart review	Mean, 11.3 (Overall)
Van Dorn, 2018*	101	DMD with normal LV function	12.0	Multicenter chart review	Mean, 5.4
Wang, 2018*	57	DMD on cardiopulmonary therapies	18.1	Single center chart review	Mean, 7.1

Abbreviations: AEs = adverse events; CINRG-DNHS = Cooperative International Neuromuscular Research Group –Duchenne natural history study; CS = corticosteroid; DMD = Duchenne muscular dystrophy; LOA = loss of ambulation; LTBP4 = Latent Transforming Growth Factor Beta Binding Protein 4; LV = left ventricular; MD STARnet = Muscular Dystrophy Surveillance Tracking and Research Network; RAAS = renin–angiotensin–aldosterone system; RU = resource use; SPP1 = Secreted Phosphoprotein 1
Note: *Mixed corticosteroid treatment status +unknown corticosteroid treatment status

Figure 2. Reported estimates of (a) mean age at LOA, (b) median age at LOA, (c) mean (median) age at death



Abbreviation: CF = cardiac failure; CP T = cardiopulmonary therapies; CS = corticosteroid; DFZ = deflazacort; DMD: Duchenne muscular dystrophy; IV = invasive ventilation; LOA: Loss of ambulation; LT = long-term; LVD = left ventricular dysfunction; NIV = non-invasive ventilation; Oth = other; RF = respiratory failure; ST = short-term; y = years

DISCUSSION

- This review synthesized estimates of the age at LOA and death among patients with DMD treated with corticosteroids.
  - Natural history studies among corticosteroid-treated patients from Canada and the US report that, on average, LOA occurs at the beginning of the second decade, and death in the third decade.
- Comparing results across studies is challenging for several reasons:
  - Changes in standards of care over time, including timing, duration and dose of corticosteroid treatment
  - Known variability in progression among patients with DMD, due to genotype
  - Heterogeneous inclusion criteria across studies
- Due to the rarity of DMD, many estimates are derived from studies with relatively small sample sizes and short follow-up.
- This was the first systematic review to summarize age at LOA and mortality among those with DMD from North America, among corticosteroid-treated patients. A better understanding of the impact of specific doses and frequencies of corticosteroid treatment, or patient genotype, will be valuable to help close the gaps in knowledge of the natural history of DMD.

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