Corticosteroids in Duchenne muscular dystrophy: impact on the motor function measure sensitivity to change and implications for clinical trials.

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***Names and affiliations of the MFM DMD corticosteroids group are included in the Acknowledgments.**

This article is commented on by Domingos and Muntoni on page 117 of this issue.

PUBLICATION DATA

Accepted for publication 24th August 2017.
Published online 9th October 2017.

ABBREVIATIONS

DMD	Duchenne muscular dystrophy
MFM	Motor function measure
MFM-32	Motor function measure with 32 exercise items
D1	Domain 1 of the MFM (standing position and transfers)
D2	Domain 2 of the MFM (axial and proximal motor function)
D3	Domain 3 of the MFM (distal motor function)
SRM	Standardized response means

AIM To monitor the evolution of the motor function of ambulatory patients with Duchenne muscular dystrophy (DMD) treated by corticosteroids for 2 years in comparison with untreated patients.

METHOD This observational, multicentre cohort study explores the evolution of the motor function measure (MFM) over a 24-month period for 29 ambulant corticosteroids-treated and 45 ambulant untreated patients with DMD.

RESULTS Significant differences were found between mean MFM scores in corticosteroids-treated and untreated groups for domain 1 of the MFM (standing position and transfers; D1), domain 2 of the MFM (axial and proximal motor function; D2), and domain 3 of the MFM (distal motor function; D3). Subscores were between 0 months and 6 months, and 0 months and 24 months. For the D1 subscore specifically, there was a significant increase in the corticosteroids-treated group (mean±standard deviation [SD] slope of change=12.6±15.5%/y), while a decrease was observed in the untreated group (−17.8±17.7%/y) between 0 months and 6 months ($p<0.001$). Sensitivity to change as assessed by standardized response means was high between 12 months and 24 months for D1 of both corticosteroids-treated and untreated groups (1.0 and 1.2 respectively), and low for D2 and D3 of both treated and untreated groups.

INTERPRETATION Patients with DMD treated by corticosteroids present a different course of the disease as assessed by MFM, confirming the sensitivity to change of the MFM in this population.

Duchenne muscular dystrophy (DMD) is a genetic recessive X-linked disease affecting skeletal muscles and myocardium. This is the most frequent muscular dystrophy in children, affecting 1 out of 5000 male live births. Several studies have demonstrated the benefit of corticosteroids for DMD, which are currently part of the care recommendation. Corticosteroids slow the decline in muscle strength and function in DMD,[1–3] and significantly increase muscular strength and timed motor and pulmonary functional tests in the short-term (6mo–2y of treatment), and delay the loss of ambulation from 2 to 5 years of treatment in the long-term.[1,3–5] Hence, international consensus recommendations that specify the appropriate follow-up and care of patients with DMD recommend the use of corticosteroids in this population.[1,5–7] Initiation of corticosteroids usually occurs between 4 years and 8 years of age, before loss of ambulation and when the plateau phase seems reached based on objective functional assessments, and optionally on report of patients or parents.[7] Some medical teams begin corticosteroid treatment even sooner, between 2 years and 4 years of age, with encouraging results. Kinali et al. had shown a well-tolerated treatment and efficacy in terms of functional scores in comparison to untreated patients, through a small DMD sample.[8]

Clinical trials in neuromuscular diseases require a rigorous approach to monitor longitudinal changes in

neuromuscular status over time. Considering that DMD causes rapid impairment of motor function, it is crucial to use a valid, reliable, feasible, and sensitive tool with established metrological properties. Starting in the 1980s, several functional tests were developed to assess motor function in patients with DMD, such as functional grades of disability (Vignos score[9] or Brooke score),[10] that provide a rapid description of patient status, but suffer from a lack of discrimination between patients and sensitivity to detect changes. Other more detailed functional tests were specifically designed for non-ambulatory (Egan Klassification scale[11]), or ambulatory patients with DMD (6-minute walk test,[12] North Star Ambulatory Assessment[13]). The latter are thus non-applicable if a loss of ambulation occurs during the longitudinal follow-up. The performance of upper limb is an outcome measure applicable across a broad spectrum of DMD disease severity, but assesses only upper limb function.[14] The motor function measure (MFM) has been developed since 1998 and is a reliable tool designed for most neuromuscular diseases encompassing DMD. It is applicable to all degrees of disease severity, in ambulatory and non-ambulatory patients, between 6 years and 60 years of age.[15] Its sensitivity to change was assessed in 152 individuals with neuromuscular disorders.[16] In DMD, there is a high prevalence of attention deficit and cognitive impairment, the impact of which on measuring motor function has to be taken into account when evaluating the validity of an outcome measure as MFM, specifically in a DMD population. MFM validity was also established in DMD corticosteroids-naive patients,[16–18] as well as in a small number of corticosteroids-treated patients for a short duration of follow-up (<2y).[17,19]

Recently, promising therapeutics such as antisense oligonucleotides have emerged in DMD, strengthening the need for validated tools monitoring longitudinal changes in neuromuscular status over time in these children. The populations involved in the current antisense oligonucleotides clinical trials are young patients with early-stage DMD treated by corticosteroids.[20] Therefore, in order to better understand the evolution of motor function of young patients with DMD under corticosteroids, in this multicentre study we investigated the ability of the MFM to detect change in motor function of patients with DMD over the first 24 months after corticosteroids implementation.

METHOD

The study is an observational, retrospective, multicentre cohort study. Ethical approval was obtained from the Comité de Protection des Personnes Lyon Sud Est II (IRB number: 00009118). Consent of participants was obtained according to the Declaration of Helsinki.

Participants

Patients originated from the MFM database. This database has been available on the Internet since 2007 and allows participating departments to securely enter MFM data pertaining to their patients (see http://www.mfm-nmd.org/).

What this paper adds

- Corticosteroids have a quantitative impact on muscle strength 6 to 24 months after starting treatment.
- Motor function measure is a valid outcome measure in Duchenne muscular dystrophy patients under corticosteroid treatment.

We applied the following inclusion criteria to set-up the two groups of the study (corticosteroids-treated and untreated groups): included patients were (1) male; (2) with DMD confirmed by molecular biology or muscle biopsy (absence of dystrophin by immunohistochemistry or Western blot analysis); (3) ambulant at baseline (a patient is considered as ambulatory if he/she is able to walk 10 steps in an indoor setting without human assistance and with or without technical assistance or devices); (4) aged at least 6 years old; (5) to be assessed during their routine follow-up by MFM with 32 exercise items (MFM-32) at least twice by a physiotherapist trained in MFM administration by a MFM training staff (see http://www.motor-function-measure.org/training-sessions.aspx), with a minimal delay of 6 months and a maximal delay of 24 months between the first and the second MFM-32.

Patients included in the corticosteroids-treated group had to be treated for 2 years using prednisone or deflazacort and had a baseline MFM-32 assessment close to corticosteroids implementation (from 4mo before to 4mo after).

Excluded patients were patients with DMD (1) participating in a clinical study that could potentially impact their motor function; (2) with intercurrent events (recent trauma, disease, or orthopaedic surgery) possibly affecting the measure of their motor function; (3) with severe mental or behavioural difficulties precluding optimal MFM-32 assessment.

Settings

From January 2007 to June 2013, 11 French departments of physical medicine and rehabilitation, neurology, and/or consultations in a reference centre for neuromuscular diseases, registered at least one patient with DMD included in this study in the MFM database.

Data collection

Follow-up visits were carried out after normal practices of participating departments. The collected data for each subsequent visit included patients date of birth where available and, for each MFM-32, date of MFM, ambulatory status, MFM scores, cooperation during MFM completion (optimal, moderate, or null), history of recent surgery (<3mo), intercurrent disease or trauma, and medication.

The MFM scale

Motor function measure is a generic scale designed to precisely monitor severity and progression of motor function in patients with any neuromuscular disease. The MFM-32 has been validated in patients aged 6 to 60 years[15] and comprises 32 items grouped in three motor function domains, as derived from a principal component analysis:

- D1: domain 1 of the MFM (standing position and transfers; 13 items);
- D2: domain 2 of the MFM (axial and proximal motor function; 12 items);
- D3: domain 3 of the MFM (distal motor function; 7 items).

The scoring of MFM uses a 4-point Likert scale based on the individual's maximal abilities. The generic grading is: 0=cannot initiate the exercise or maintain the starting position; 1=performs the task partially; 2=performs the movement incompletely, or completely but imperfectly (compensatory movements, position maintained for an insufficient duration of time, slowness, uncontrolled movement); and 3=performs the task fully and 'normally'.

Total score and D1, D2, and D3 subscores are expressed as a percentage of the maximum possible score; the lower the total score, the more severe the impairment.

Statistical analysis

Quantitative variables were described using means, standard deviations (SD), and intervals. Qualitative variables were described using numbers and percentages. Mean and SD were also used to compare the age at loss of walking ability between corticosteroids-treated and untreated groups. The level of statistical significance was set at a p value of less than 0.050.

The change in scores was studied according to the patient group (corticosteroids-treated and untreated) by analysing the slopes of change in patients. For each patient, the repeated measurements of MFM scores were summarized by a slope of change expressed as an annual rate using the unweighted least-square estimate.[21] Because the assumption of normal distribution of MFM scores is in doubt, a nonparametric Mann–Whitney U test was used to compare the change in MFM scores in the corticosteroids-treated and untreated groups, a nonparametric Wilcoxon signed-rank test was used to compare slope of change of corticosteroids-treated patients at two different time points, and a χ^2 test was used to compare the proportion of patients losing the ability to walk in corticosteroids-treated and untreated groups.

Standardized response means (SRM) were obtained by calculating the ratios of the mean slopes to their SDs. SRM values were considered high if greater than or equal to 0.80, moderate if ranging from 0.50 to 0.79, and low if less than 0.50.[22]

RESULTS

Group characteristics

A total of 195 patients with confirmed DMD were registered in the MFM database. Among them, 74 ambulatory males met the inclusion criteria at baseline: 29 in the corticosteroids-treated group (mean age±SD [range]: 7.99±1.48y [6–11.33y]) and 45 in the untreated group (mean age±SD [range]: 7.91±1.52y [5.92–11.83y]; Table I). Patients from the untreated group mainly originated from an historical cohort of patients constituted before the large introduction of the corticosteroid treatment in France. Four males with DMD whose parents refused corticosteroid treatment were also included in the untreated group. At baseline, both groups were not significantly different regarding age, age at onset of walking, and MFM scores (Table I).

Follow-up

Follow-up data were obtained for 13, 23, and 17 patients for the untreated group and 22, 28, and 24 patients for the corticosteroids-treated group at 6 months, 12 months, and 24 months respectively.

Patients under corticosteroid treatment were mainly treated by prednisone, except for one patient treated by deflazacort. The most frequent implementation dose was 0.75mg/kg/day prednisone (22 out of 29 patients), and 10 patients had a dose adjustment during their follow-up, moving from a daily dose to a dose every other day (Table II). Corticosteroids implementation age was under 7 years for 10 patients and above 7 years for 19 patients.

During the 24-month follow-up, 23 patients lost the ability to walk (Table II): 16 in the untreated group and 7 in the corticosteroids-treated group (35.6% vs 24.1%, χ^2 test: p=0.300). None of the 10 patients of the corticosteroids-treated group aged less than 7 years at inclusion

Table I: Patient characteristics and motor function measure scores at baseline for corticosteroids-treated and untreated Duchenne muscular dystrophy populations

	Untreated group	Corticosteroids-treated group	Mann–Whitney U tests
n	45	29	
Age (y)	7.91±1.52 [5.92–11.83]	7.99±1.48 [6–11.33]	0.812
Age at onset of walking (mo)	17.15±4.73 [11–36]	17.71±5.31 [9–36]	0.469
MFM scores			
TS (%)	75.23±7.65 [64.58–89.58]	76.73±9.44 [78.13–91.67]	0.381
D1 (%)	51.40±13.90 [23.08–79.49]	54.38±17.37 [17.95–84.62]	0.488
D2 (%)	94.01±4.99 [77.78–100]	94.54±5.87 [77.78–100]	0.447
D3 (%)	87.30±9.42 [47.62–100]	87.68±8.68 [66.67–100]	0.960

Values=mean±SD [range]; Mann–Whitney U tests (p>0.050), all statistically non-significant. MFM, motor function measure; TS, total score; D1, domain 1 of the MFM (standing position and transfers); D2, domain 2 of the MFM (axial and proximal motor function); D3, domain 3 of the MFM (distal motor function).

Table II: Patient follow-up over the 24-month follow-up: dose of corticosteroid treatment used and number and mean age at loss of ambulation

	n	CS implementation dose	Change in CS dose during follow-up	Loss of ambulation, *n*	Mean age at loss of ambulation, years±SD
CS-treated group	7	Prednisone 0.75mg/kg/d	Prednisone 1mg/kg every 2d	2	10.35±0.2
	3	Prednisone 0.75mg/kg/d	Prednisone 0.75mg/kg every 2d	1	10.75
	5	Prednisone 1mg/kg every 2d	No	2	10.5±0.5
	12	Prednisone 0.75mg/kg/d	No	2	11±1
	1	Prednisone 0.5mg/kg every 2d	No	0	NA
	1	Deflazacort 0.75mg/kg/d	No	0	NA
Untreated group	45	NA	NA	16	9.2±1.8

Values=mean±SD. CS, corticosteroids; NA, not applicable.

lost the ability to walk during the 24-month follow-up and five from the 18 patients of the untreated group aged less than 7 years at inclusion lost the ability to walk during the 24-month follow-up.

MFM evolution

MFM scores worsened for a majority of patients of the untreated group during the 24-month follow-up (76.9% for D1, 61.5% for D2, and 53.8% for D3 between 0 months and 6 months, and 80% for D1, 60% for D2, and 60% for D3 between 12 months and 24 months; Fig. 1).

For the corticosteroids-treated group, a majority of patients had an improved D1 score between 0 months and 6 months (81.8%), followed by a worsening of this score between 6 months and 12 months and between 12 months and 24 months (80.9% and 81.8% respectively). Whereas D2 and D3 scores of these corticosteroids-treated patients improved for a majority of patients between 0 months and 6 months (54.5% and 59.1% respectively), these scores tended to not change afterwards (at least 42.8% of patients had no change of D2 or D3 scores between 6 months and 12 months or between 12 months and 24 months).

Between 0 months and 6 months, as well as between 0 months and 24 months, significant differences were found between corticosteroids-treated and untreated patients for all mean MFM scores annual slopes of change (Table III). Whereas all MFM scores decreased in the untreated group in agreement with the disease progression, all MFM scores increased or remained almost stable between 0 months and 6 months or between 0 months and 24 months in the corticosteroids-treated group (Table III).

In the corticosteroids-treated group, an increase in motor function was observed for D1 between 0 months and 6 months (mean±SD slope of change=12.6±15.5%/y) (Table III). After 6 months, post-corticosteroids implementation, the D1 score decreased with time, with similar slopes of change between 6 months and 12 months and between 12 months and 24 months (mean±SD: −12.2±14.5%/y vs −11.9±12.2%/y respectively, Wilcoxon signed-rank test: p=0.990). D2 and D3 scores continued to increase between 6 months and 12 months of corticosteroids. Between 0 months and 24 months a slight decrease of D1 was noticed in the corticosteroids group (mean±SD: −4.8±7.6), whereas there was a large deterioration of D1 in the untreated group (mean±SD: −18.8±7.1). The mean annual slope of change of the MFM subscores between 12 months and 24 months were not significantly different between the corticosteroids-treated and untreated group (D1: p=0.206, D2: p=0.343, D3: p=0.154).

Sensitivity to change

Sensitivity to change as assessed by SRM was high between 12 months and 24 months for D1 of both corticosteroids-treated and untreated groups (1.0 and 1.2 respectively), and low for D2 and D3 of both treated and untreated groups (SRM between 0.2 and 0.5; Table III). Regarding MFM total score, significant differences were found between 0 months and 6 months, and 0 months and 24 months between both groups, with a slower decrease with time in corticosteroids-treated patients than in untreated patients. Values of SRM were large between 0 to 6 months for corticosteroids-treated and untreated patients (0.8 and 0.9 respectively; Table III), they remained large between 0 months and 12 months, and 0 months and 24 months (1.0 and 2.4 respectively) only in the untreated group.

DISCUSSION

This study is based on data from an existing MFM database. Follow-up visits were not imposed by a protocol but performed according to the usual care of participating departments. This explains the limited number of patients enrolled in the study and that all patients do not have data for all visits. Consequently, we are cautious about results analysis and conclusions.

Corticosteroid treatment is known to improve motor function.[1–3] Hence, it has been previously reported that corticosteroids stabilized motor function measured by the MFM in 12 corticosteroids-treated patients compared with a control group of 12 untreated patients over a 12-month period,[17] and that corticosteroids improved motor function over 6 months in 22 patients in comparison to baseline.[19] In the present study, significant differences in MFM scores between corticosteroids-treated and untreated patients during follow-up were observed. This reinforces the evidence that corticosteroids change the natural history of the disease and that MFM is sensitive enough to be able to detect

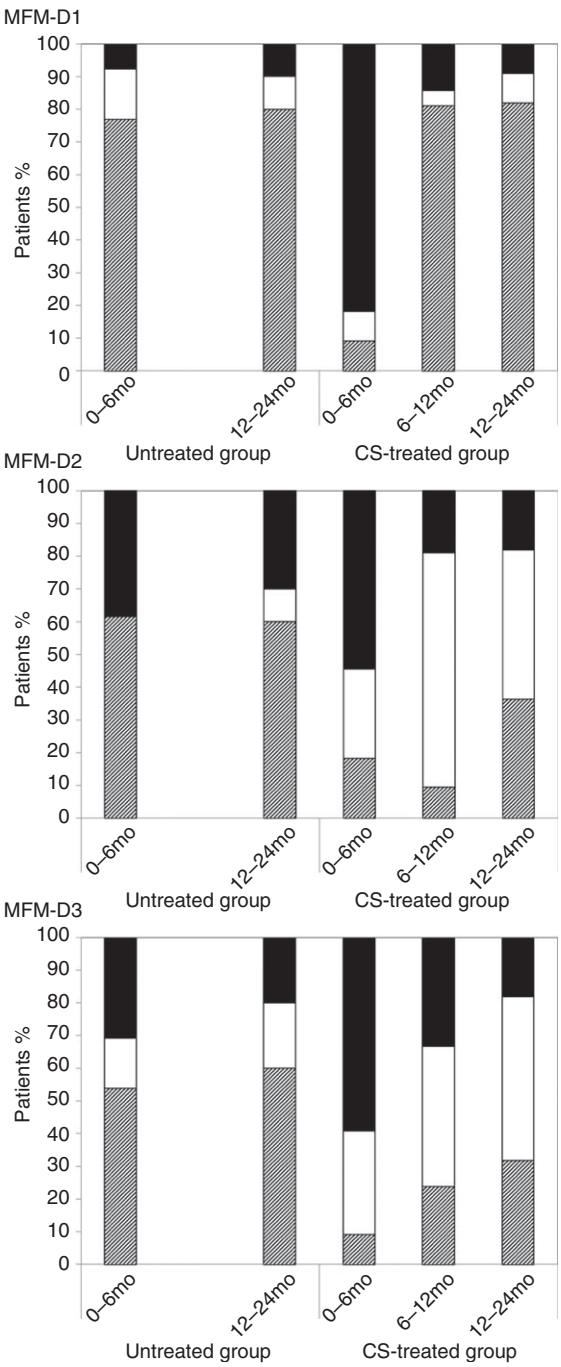

Figure 1: Percentage of patients from untreated group or corticosteroids-treated (CS-treated) group showing improvement (black bar), no change (white bar), or decrease (hatched bar) of MFM score domain 1 of the MFM (standing position and transfers), domain 2 of the MFM (axial and proximal motor function), and domain 3 of the MFM (distal motor function) during the patients follow-up. Results for untreated group were obtained from 13 patients for the 0–6mo period and 10 patients for the 12–24mo period. Results for the CS-treated group were obtained from 22 patients for the 0–6mo period, 21 patients for the 6–12mo period, and 22 patients for the 12–24mo period.

change in the functional status of the patients with DMD treated by corticosteroids.

In our study, an increase in D1 score, corresponding to an improvement of standing position and transfer motor function capacities in a 6-month period, was observed in the corticosteroids-treated group. This contrasted with the continuous decline of motor function in the untreated group and confirmed results of a previous study that investigated an ambulant and non-ambulant population with DMD over a short period.[19] After 12 months, a continuous deterioration of D1 score was observed in the treated group but at a lower rate than that observed in the untreated group, suggesting a positive impact of corticosteroids on D1, even during the D1 deterioration phase. The mean annual slope of change of D1 was relatively shallow between 0 months and 12 months; the increase in D1 score from 0 to 6 months was probably compensated by the decrease observed from 6 to 12 months, with the overwhelming majority of patients having a decrease in D1 score during this time period. Regarding D2 and D3, an increase of both MFM subscores was observed over the first 12 months, reflecting an improvement in distal motor function induced by treatment, as previously shown by da Silva et al.[19] but over the subsequent 12-month period they decreased at a lower rate than that of untreated patients. Yet the difference in the decrease did not reach statistical significance precluding any conclusion as to a positive effect of corticosteroids on MFM slope of change after 12 months.

In addition, over a 24-month period, significant differences were found between corticosteroids-treated and untreated patients for all mean MFM scores and annual slopes of change. Fewer patients lost their ability to walk in the corticosteroids-treated group than in the untreated group during the 24 months of follow-up (24.1% vs 35.6% respectively); however, this did not reach statistical significance. All patients having lost the ability to walk from the corticosteroids-treated group were aged at least 7 years old at inclusion and 37.5% of patients having lost the ability to walk from the untreated group were aged less than 7 years old at inclusion. For patients under corticosteroids after the loss of the ability to walk, MFM changes over time are important to look into, especially as D2 and D3 subscores allow following patients after loss of ambulation. As a result of the shortness of the follow-up, no longitudinal data are available for patients having lost ambulation. This will be the subject of a new study.

Steeper slopes of change were observed in D1 than for the other subscores, which was expected for a DMD population exclusively composed of young ambulant patients. The D1 subscore has been shown to be the most informative dimension at this stage of the disease to evaluate change with the possibility to predict the loss of walking ability.[17,19,23] D1 subscore explores not only the ability to walk but also the ability to stand and to transfer from

Table III: Evolution of corticosteroids-treated or untreated patients assessed by motor function measure during the 24-months follow-up

	Untreated group				CS-treated group				
	n	MFM scores at first MFM of the time period (%)	Mean slopes of change (%/y)	SRM	*n*	MFM scores at first MFM of the time period (%)	Mean slopes of change (%/y)	SRM	*p*[a]
TS (total score)									
0–6mo	13	73.8±10.2	−8.8±10.1	0.9	22	78.6±9.3	+8±9.9	0.8	<0.001
0–12mo	23	76.9±7.6	−7.7±7.8	1	28	77.5±9.6	+1.1±7	0.2	<0.001
6–12mo	0	–	–	–	21	83.0±9.0	−4.1±7.1	0.6	NA
12–24mo	10	72.6±5.2	−8.6±6.6	1.3	22	80.2±10.7	−5.4±5.5	1	0.084
0–24mo	17	77.5±5.3	−9.4±4	2.4	24	77.5±8.9	−1.4±3.6	0.4	<0.001
D1 (standing and transfers)									
0–6mo	13	51.5±16.1	−17.8±17.7	1.0	22	58.2±17.1	+12.6±15.5	0.8	<0.001
0–12mo	23	54.5±12.9	−15.5±15.1	1.0	28	56.4±17.5	−1.1±12.3	0.1	<0.001
6–12mo	0	–	–	–	21	65.0±18.1	−12.2±14.5	0.8	NA
12–24mo	10	42.6±14.6	−17.2±14.4	1.2	22	58.5±20.1	−11.9±12.2	1.0	0.206
0–24mo	17	55.7±9.3	−18.8±7.1	2.6	24	56±16.3	−4.8±7.6	0.6	<0.001
D2 (axial and proximal motor capacities)									
0–6mo	13	91.7±6.3	−1.7±8.9	0.2	22	94.9±5.1	+3.8±10.1	0.4	0.026
0–12mo	23	94.4±5.6	−3.7±7.1	0.5	28	94.4 ±5.9	+1.6±5.3	0.3	<0.001
6–12mo	0	–	–	–	21	97.2±4.1	+0.5±4.3	0.1	NA
12–24mo	10	93.3±4.2	−2.5±5.1	0.5	22	97.0±5.1	−1±4.2	0.2	0.343
0–24mo	17	94.6±4.5	−4.4±3.5	1.3	24	95.4±5.4	+0.5±1.9	0.3	<0.001
D3 (distal motor capacities)									
0–6mo	13	84.6±13.5	−4.4±13.8	0.3	22	88.3±8.7	+6.9±15	0.5	0.011
0–12mo	23	88.2±11.2	−0.2±8.4	0	28	87.4±8.7	+4.3±8.0	0.5	0.026
6–12mo	0	–	–	–	21	92.1±6.3	+3.2±10.6	0.3	NA
12–24mo	10	92.9±4.6	−1.9±6.8	0.3	22	91.6±8.6	−0.9±4.6	0.2	0.154
0–24mo	17	88.5±7.5	−0.6±4.2	0.1	24	86.9±9.1	+1.8±4.1	0.4	0.019

[a]Mann–Whitney *U* test between the change in MFM scores of corticosteroids-treated and untreated groups. MFM scores are expressed in mean %±SD. CS, corticosteroids; MFM, motor function measure; SRM, standardized response means; TS, total score; NA, not applicable; D1, domain 1 of the MFM (standing position and transfers); D2, domain 2 of the MFM (axial and proximal motor function); D3, domain 3 of the MFM (distal motor function).

standing to sitting, which are interesting functional abilities in this stage of the disease.

Although this study should be replicated in a different cohort to improve the robustness of the results, we strongly recommend consideration of MFM as an outcome measure in clinical trials including ambulatory patients with DMD treated with corticosteroids, especially as SRM values of at least 0.8 for the D1 subscore were observed after 6 months of corticosteroid treatment, confirming that this subscore was the most sensitive to change in this population. Conversely, SRM values were found to be low for D2 and D3 after 12 months of corticosteroid treatment, indicating that these are of poor interest to investigate the early stages of the disease, but they do remain of use in the later stages of the disease, particularly for D3.[24] The advantage of D2 and D3 subscores are that they allow for the monitoring of patients with long-term follow-up, for example during post-marketing drug effect monitoring, when patients have lost the ability to walk.

As a result of a 4-point scoring system, a precise measurement of MFM items is obtained for children with optimal cooperation and respect of instructions. In addition, some MFM items, particularly items of D3, could be influenced by coordination and cognitive development in a young population. In this study, in order to have more homogenous data, only MFM with a patient's optimal cooperation and MFM completed by a trained therapist were taken into account. In fact, the level of cooperation by the patient during the realization of the MFM could be improved when carried out by a therapist experienced with priority in the paediatric domain. Care should thus be taken in generalizing our findings in a general population of DMD.

When planning a clinical trial involving corticosteroids-treated patients with DMD and in which the MFM is an outcome measure, in order to avoid a differential effect of corticosteroids, we suggest including patients at least 6 months after corticosteroids implementation if the D1 subscore is the only component considered, and at least 12 months after corticosteroids implementation if D2 and D3 are also considered.

Study limitations

The small sample size could be considered as a study limitation, particularly because of the high clinical variability among males with DMD, in addition to the retrospective design and consequently missing data for the untreated patients between 6 months and 12 months.

Untreated patients were part of a historical cohort, mainly constituted before the widespread treatment of children with DMD by corticosteroids in France; because of proven medical benefits of corticosteroids a placebo group could not be established. Major differences in the management of patients could have an implication for the interpretation of the outcome of the study. In our study, we only considered patients from 6 years of age, because of the use of MFM-32. The same type of study should be carried out in younger patients using MFM-20, which is a shorter form of the MFM scale validated for children from 2 to 6 years of age.[25]

ACKNOWLEDGEMENTS

We thank the MFM DMD Corticosteroids Group: Sylviane Peudenier and Juliette Ropars (Hôpital Morvan, CHRU de Brest); Andoni Urtizberea (Hôpital marin, AP-HP, Hendaye); Vincent Tiffreau (Hôpital Pierre Swynghedauw, CHRU de Lille); Blandine Puyhaubert (Pôle Femme-Mère-Enfant, CHRU de Montpellier); Manuella Fournier Mehouas et Catherine Fafin (Hôpital l'Archet, CHU de Nice); Sabrina Sacconi (INSERM Unité 638, Institut Fédératif de Recherche 50, CHU de Nice); Emmanuelle Lagrue (Hôpital pédiatrique Gatien de Clocheville, CHRU de Tours); Stéphane Chabrier (Hôpital Bellevue, CHU de Saint-Etienne).

We acknowledge Philip Robinson from DRCI of Hospices Civils de Lyon for his critical and English review. The authors have stated that they had no interests which might be perceived as posing a conflict or a bias.

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