Monitoring changes and predicting loss of ambulation in Duchenne muscular dystrophy with the Motor Function Measure

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AIM To assess changes in motor function in patients with Duchenne muscular dystrophy using the Motor Function Measure (MFM).

METHOD Three studies were performed. Two studies included only physiotherapy-treated patients, with 13 patients (males mean age 11y 7mo, SD 1y 10mo, range 8–14y) in the 3-month study and 41 patients (males mean age 14y 1mo, SD 5y 5mo, range 6–32y) in the 1-year study. A third study compared 12 patients treated with steroids with 12 age- and motor-function-matched untreated patients (males mean age of treated patients 10y 2mo, SD 2y 2mo range 6–14) over a 12-month period.

RESULTS Over 3 months, the MFM D1 subscore (standing and transfers) decreased significantly (−4.7%; p=0.01). Over 1 year, all MFM subscores decreased significantly: −4.9% for D1 (p<0.01); −7.7% for D2 (axial and proximal motor capacity; p<0.01); −4.3% for D3 (distal motor capacity; p=0.03); and −5.8% for the total score (p<0.01). A threshold value for loss of ambulation and a predictive value 1 year before loss were estimated (total score 70% and D1 subscore 40%). Compared with the controls, patients treated with steroids had more stable total scores (−0.59 vs −5.87; p=0.02) and D2 subscores (0.98 vs −8.50; p<0.01).

INTERPRETATION These results support the use of the MFM in everyday patient management to prepare for loss of ambulation and in clinical trials to follow up patients receiving various treatments.

Duchenne muscular dystrophy (DMD) is one of the most frequent neuromuscular pathologies seen in paediatric rehabilitation.1 The early stages of motor decline in DMD are already well known, including the loss of ability to walk that occurs on average around the age of 9 years.2 However, after that age the changes in motor capacity in children and adolescents with DMD have been insufficiently investigated. This is especially true for upper-limb function. Monitoring motor changes in patients with DMD requires functional evaluation along with measurement of muscle strength.3

The Motor Function Measure (MFM) is a tool designed recently for neuromuscular diseases and is applicable to all degrees of disease severity in ambulant and non-ambulant patients. It was validated in terms of reproducibility, construct validity, and concurrent validity.4 Its sensitivity to change has also been assessed at a 1-year interval in 152 patients with various neuromuscular disorders. There was a good correlation between MFM score changes and self-rated or investigator-rated disability changes.5 The need for a reliable outcome measure in diseases of rapid deterioration such as DMD led us to analyse the efficiency and the sensitivity to change of the MFM, especially during the loss of ability to walk. We attempted to answer the following three questions: (1) Is the sensitivity of the MFM scale sufficient to detect changes in motor function in patients receiving no other treatment than physiotherapy over a short period of 3 months or a medium period of 1 year? (2) Is it possible to detect differences over only 1 year between a group of patients treated with steroids and an untreated control group? (3) Is the MFM able to predict loss of ambulation 1 year before its occurrence in order to allow time to adapt rehabilitation, change the patient’s environment, and consider acquisition of assistive aids?

METHOD Participants

Patients were enrolled in 17 rehabilitation or neuromuscular centres: 16 French and one Swiss. The single inclusion condition was a diagnosis of DMD confirmed by genetic analysis or...
The motor function measure
The MFM is used by physiotherapists or physicians to assess motor capacity in patients with various neuromuscular diseases. The scale assesses the motor function of patients whatever the reason for the impairment (pain, joint limitation, or decreased strength). It was validated in 2004 in 303 patients aged 6 to 60 years, of whom 72 had DMD.6

The MFM consists of 32 items (tasks) classified into the following three dimensions: D1, standing and transfers; D2, axial and proximal motor capacity; and D3, distal motor capacity. Each item is scored on a four-point Likert scale. The generic grading is measured as follows: 0, cannot initiate the task or cannot maintain the starting position; 1, partially performs the task; 2, performs the task with compensatory movements (position maintained for an insufficient period of time, slowness, uncontrolled movements, etc.); and 3, performs the task fully and ‘normally’, the movement being controlled, mastered, directed, and performed at a constant speed.

The method of scoring each item is detailed in the User’s Manual, available in English, French, and Spanish (down-loadable from http://www.mfm-nmd.org). The 32 scores are summed to yield a total score expressed as a percentage of the maximum possible score (no physical impairment): the lower the score, the more severe the impairment. In addition, the three subscores (D1, D2, and D3) provide a more detailed profile of the physical impairment.

All tests were administered by physiotherapists trained in the MFM. It took an average of 36 minutes to perform the whole MFM.

The studies
Three studies were performed. The first two involved 49 patients with confirmed DMD who were receiving no treatment other than physiotherapy. Five patients participated in both studies (Fig. S1, supporting information, published online).

The short-term study was carried out between November 2004 and March 2005. It included 13 patients examined twice, at 3-month intervals by design. The mean interval between the two MFMs was 3 months 11 days (SD 14d). At the first MFM, the mean age was 11 years 7 months (range 8–14y) and four among these patients were still ambulant.

The medium-term study was carried out between May 2002 and July 2004. It included 41 patients examined twice, at 1-year intervals by design. The mean interval was 16 months 2 days (SD 2mo 19d). At the first MFM, the mean age of the patients was 14 years 1 month (range 6–32y) and 11 patients were ambulant.

The third study was carried out between April 2005 and March 2007. It compared 12 patients using steroids (of whom four were previously enrolled in the above medium-term study) with 12 untreated age- and motor-function-matched patients with DMD. At first MFM, the mean age of the 12 treated patients was 10 years 2 months (range 6–14y), of whom six were ambulant. Among the untreated patients, five were ambulant.

The three studies were approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale Lyon A (France) and the ethics committee of Lausanne University (Switzerland). The participants or their legal representatives signed a consent form and an information sheet on the study protocol.

Statistical analysis
Only complete data sheets were used in the analysis (no missing data). The means and interquartile ranges of MFM scores (D1, D2, D3, and total score) were calculated and displayed graphically using box plots. Ages were reported as means and ranges. In each patient, the change in a given MFM score was the difference between end of follow-up and baseline scores. The mean score change (with SD) was then calculated within each dimension. In the medium-term study, because of the different follow-up periods (11–22mo), individual scores were transformed by linear interpolation into annual (12mo) score changes. The mean change within each group (13 or 41 patients) was tested (vs zero) using the non-parametric Wilcoxon two-tailed test and comparisons of changes between groups were made using the Mann–Whitney U two-tailed test. In all comparisons, the significance level was set at 0.05 (two-tailed).

The sensitivity to change of the MFM scores between baseline and end of follow-up was assessed using the standard response mean, defined as the mean score change divided by the SD of that score change.7

Effect sizes were used to compare the subscores and total score of patients treated with steroids to those of untreated controls. The effect size was defined as the mean change in score among treated patients minus the mean change among untreated patients divided by the SD of the changes in the untreated group.

The standard response mean and the effect size can be easily interpreted using Cohen’s rule of thumb, which ranks the sensitivity to change into small (0.2–0.49), medium (0.50–0.79), and large (≥0.80).8 Data were analysed with Statview software 5.0 Adept Scientific Inc., Acton, MA, USA.

RESULTS
Mean score change in short-term and medium-term studies
The cooperation of the patients was rated ‘excellent’ in all cases except one, who was rated ‘good’ in the 3-month study.
The total MFM scores at baseline of all 49 participants according to age are presented in Figure 1. The curve that fits the data shows an exponential decrease in the total score with age (equation: total MFM score = 211.13 exp[−0.136 age]). A total score of 58% would separate ambulant from non-ambulant patients whatever their age.

In the short-term study, the only significant mean score change between baseline and end of follow-up was that of D1 (−4.7%; p<0.01; Table I). In the medium-term study, all subscores (D1, D2, and D3) and the total score showed significant mean score changes between baseline and end of follow-up. These changes were −4.9% for D1 (p<0.01), −7.7% for D2 (p<0.01), −4.3% for D3 (p=0.03), and −5.8% for the total score (p<0.01).

In the medium-term study, in the 11 patients able to walk at baseline, the mean score change was −17.2% for D1 (SD 14.1; range −34.2 to 13.9%) and −7.9% for the total score (SD 6.0; range −14.6 to 6.8%). In the 30 patients unable to walk at baseline, the mean score change was −9.4% for D2 (SD 12.5; range −48.9 to 11.7%) and −5.0% for the total score (SD 6.3; range −19.3 to 5.3%). Concerning the 16 patients aged over 14 at baseline, the mean score change was −3.9% for D2 (SD 8.1; range −16.6 to 11.7%), −10.8% for D3 (SD 18.5; range −66.1 to 19%), and −3.9% for the total score (SD 6.4; range −19.3 to 5.2%).

The individual changes in scores according to age and walking ability showed that D1 could be of interest before loss of ambulation because D2 and D3 remained stable before that loss. Indeed, D2 (Fig. 2) declined at about the time of loss of ambulation (by 10y of age) and D3 (Fig. S2, supporting information, published online) at later stages (after 15y of age).

### Patients treated with steroids versus untreated patients

Significant differences in the mean score change were found in the total score (−0.6% vs −5.9%, p=0.02) and in subscore D2 (1.0% vs −8.5%; p<0.01) between patients treated with steroids and untreated patients. Furthermore, MFM scores were relatively stable in the patients treated with steroids (Table II).

### MFM sensitivity to change

The standard response means in the short- and medium-term studies are given in Table I. In the short-term study, the values of the standard response means of all scores were medium (all <0.49): the MFM is unable to detect only slight changes at 3-month intervals. However, at 12 months, the standard response mean of the total score was large (0.86), whereas that of D2 was medium (0.68).

The effect sizes (Table II) were large (>1) for the total score and D2 but small for D1 and D3.

Thus, the MFM can be considered sufficiently sensitive to detect changes in the total score over a 1-year span.

### Loss of ability to walk

Thirty-four out of the 49 patients (in the short- and medium-term studies) lost their ability to walk at a mean age of 9 years.
5 months (range 6–14y). In the medium-term study, six out of 11 patients ambulant at baseline lost their ability to walk between 7 and 12 years of age. Using a linear interpolation from the observed MFM scores of these six patients, we estimated the hypothetical scores at the time of loss of ambulation to be 63.6% (range 54.7–70.8%) for the total score and 25.0% (range 16.7–33.3%) for D1. The MFM value that would predict loss of ambulation 1 year before it occurs can be estimated using the mean score change at 12 months in the 11 ambulant patients. That value can be rounded to 40% for D1 (25% hypothetical score + 17.2%, the 1y mean change) and to 70% for the total score (63.6% hypothetical score + 7.9%, the 1y mean change).

The individual scores declined according to age over a 1-year period in the 41 medium-term study patients shown in Figure 2. One particular case was worth noticing because of sharp rises or drops in the MFM scores. Specifically, the changes relative to this patient were very different from those of other patients with DMD involved in the study. His phenotype was less serious despite a confirmed diagnosis of DMD (deletions in exons 5–7 within the dystrophin gene). This patient lost his ability to walk when he was 14-years-old and his total score had decreased by only 1.0% over the previous 19 months.

DISCUSSION
In our sample of patients with DMD, the measures of motor function by MFM showed a continuous and exponential decline with age, which is in agreement with previous results on change in muscle strength in DMD.9,10 However, to monitor progression of DMD, evaluations of motor function are needed as a complement to measurements of muscle strength.3 Indeed, the MFM can be administered to ambulant and non-ambulant patients and each of its dimensions used to establish profiles of physical impairment and changes over time. This is an advantage over current tests of functional ability, such as

**Table II:** D1, D2, D3 values and total score completed at baseline and score change over a 12-month period in 12 patients treated with steroids versus 12 untreated Duchenne muscular dystrophy (DMD) patients

<table>
<thead>
<tr>
<th></th>
<th>Scores at baseline</th>
<th>Mean score changes</th>
<th>Effect size</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1 (standing and transfers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-treated DMD patients</td>
<td>25.0 (29.0)</td>
<td>−3.6 (8.1)</td>
<td>0.31</td>
<td>0.71</td>
</tr>
<tr>
<td>Untreated DMD patients</td>
<td>18.0 (22.8)</td>
<td>−7 (11.1)</td>
<td></td>
<td></td>
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<tr>
<td>D2 (axial and proximal motor capacities)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-treated DMD patients</td>
<td>76.3 (17.8)</td>
<td>1.0 (5.3)</td>
<td>1.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Untreated DMD patients</td>
<td>76.2 (18.4)</td>
<td>−8.5 (7.8)</td>
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<tr>
<td>D3 (Distal motor capacity)</td>
<td></td>
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<tr>
<td>Steroid-treated DMD patients</td>
<td>81.7 (11.8)</td>
<td>2.4 (4.8)</td>
<td>0.19</td>
<td>0.27</td>
</tr>
<tr>
<td>Untreated DMD patients</td>
<td>81.0 (8.9)</td>
<td>0.7 (9)</td>
<td></td>
<td></td>
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<tr>
<td>Total score</td>
<td></td>
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<tr>
<td>Steroid-treated DMD patients</td>
<td>56.7 (19.1)</td>
<td>−0.6 (4.6)</td>
<td>1.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Untreated DMD patients</td>
<td>53.2 (15.8)</td>
<td>−5.9 (5.1)</td>
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</tr>
</tbody>
</table>

Values are mean (SD). *Two-tailed Mann–Whitney U test, steroid-treated versus untreated.
timed tasks, which are informative only a short period before loss of ambulation. According to Allsop and Ziter, "Current tests of functional ability are poor measures of disease progression during most of the ambulatory period, as efficiency is maintained despite continuous decline in muscle strength." 

Besides, functional grades, such as the lower-limb score of Vigano et al. and the upper-limb score of Brooke et al., focus only on one part of the body and their scores are probably not very sensitive to change. To our knowledge, with the exception of the Hammersmith Motor Ability Scale, designed for ambulant patients, and the EK scale, designed for non-walking patients, no scale other than the MFM measures motor function in patients with DMD, ambulant or not, whose sensitivity to change is known. Moreover, the acceptance of the MFM among children was good, its administration time was relatively short (36 min on average), and its interrater variability to change is known. However, the acceptance of the MFM among children was good, its administration time was relatively short (36 min on average), and its interrater variability was ‘good’ to ‘excellent’ for most items.

The present results are also promising regarding the use of the MFM in clinical trials to demonstrate either deterioration of a patient’s condition or a possible improvement due to a specific treatment. If short test forms are needed, we suggest using D1 in younger patients who have not lost ambulation and D2+D3 in non-ambulant patients. Furthermore, the present results make it possible to estimate the number of patients to include in a prospective clinical trial. The number depends on the study design, the required power, the hypothesis concerning the outcome, and the patients’ ability to walk. For example, in a hypothesis of no change in motor function over 1 year in the active treatment group versus the control group, with 5% alpha risk and 90% power, 15 patients per group are needed for either total score or D1 score in walking patients, but 45 patients per group are needed for total score or 50 patients per group for D2 score in non-walking patients. In a hypothesis of 50% reduction in the mean score change over 1 year in the active treatment group versus the control group, with 5% alpha risk and 90% power, 70 patients per group are needed in walking patients but 190 patients per group for total score or 170 patients per group for D2 score in non-walking patients.

The two main limitations of our study are the small sample sizes and the lack of an intermediate test at 6 months. We hope further studies will confirm the ability of the MFM to detect changes over 6 months, to predict loss of ambulation in a larger number of patients, and to be used in clinical trials to demonstrate intervention effects.

APPENDIX

Members of the MFM Collaborative Study Group

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of this article:

Figure S1: Graphical representation of the study groups and subgroups.

Figure S2: Changes in motor function measure (MFM) subscore D3 (distal motor capacity) at 1-year design interval according to age in the 41 patients in the long-term study.

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REFERENCES