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Characterization of pulmonary function in 10–18 year old patients with Duchenne muscular dystrophy

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Abstract

Pulmonary function loss in patients with Duchenne muscular dystrophy (DMD) is progressive and leads to pulmonary insufficiency. The purpose of this study in 10–18 year old patients with DMD is the assessment of the inter-correlation between pulmonary function tests (PFTs), their reliability and the association with the general disease stage measured by the Brooke score. Dynamic PFTs (peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory volume in one second [FEV1]) and maximum static airway pressures (MIP, MEP) were prospectively collected from 64 DMD patients enrolled in the DELOS trial (ClinicalTrials.gov, number NCT01027884). Baseline PEF percent predicted (PEF%p) was <80% and patients had stopped taking glucocorticoids at least 12 months prior to study start. At baseline PEF%p, FVC%p and FEV1%p correlated well with each other (Spearman's rho: PEF%p–FVC%p: 0.54; PEF%p–FEV1%p: 0.72; FVC%p–FEV1%p: 0.91). MIP%p and MEP%p correlated well with one another (MIP%p–MEP%p: 0.71) but less well with PEF%p (MIP%p–PEF%p: 0.40; MEP%p–PEF%p: 0.41) and slightly better with FVC%p (MIP%p–FVC%p: 0.59; MEP%p–FVC%p: 0.74). The within-subject coefficients of variation (CV) for successive measures were 6.97% for PEF%p, 6.69% for FVC%p and 11.11% for FEV1%p, indicating that these parameters could be more reliably assessed compared to maximum static airway pressures (CV for MIP%p: 18.00%; MEP%p: 15.73%). Yearly rates of PFT decline (placebo group) were larger in dynamic parameters (PEF%p: −8.9% [SD 2.0]; FVC%p: −8.7% [SD 1.1]; FEV1%p: −10.2% [SD 2.0]) than static airway pressures (MIP%p: −4.5 [SD 1.3]; MEP%p: −2.8 [SD 1.1]). A considerable drop in dynamic pulmonary function parameters was associated with loss of upper limb function (transition from Brooke score category 4 to category 5). In conclusion, these findings expand the understanding of the reliability, correlation and evolution of different pulmonary function measures in DMD patients who are in the pulmonary function decline phase.

Keywords: Duchenne muscular dystrophy; pulmonary function; forced vital capacity; peak expiratory flow

1. Introduction

Duchenne muscular dystrophy (DMD), the most common and severe form of muscular dystrophy, is characterized by progressive respiratory muscle weakness which causes restrictive respiratory disease, impaired clearance of airway secretions, recurrent pulmonary infections due to ineffective cough, hypoventilation and eventually respiratory failure [1–4]. Routine use of glucocorticoids (GCs), the introduction of mechanical insufflation–exsufflation devices to improve airway clearance and non-invasive ventilation to ameliorate alveolar hypoventilation have become standard of care, which together have increased the average life expectancy in DMD patients [5–9]. Interestingly, a study of all-cause mortality showed that the number of deaths due to respiratory failure was not significantly influenced by the GC use status of patients [10].

Serial assessment of pulmonary function is a critical element of recommended routine monitoring for patients with DMD, as it may enable early identification and treatment of pulmonary complications [11,12]. According to standard of care recommendations [13] spirometry is required every 6 months, recording dynamic pulmonary function parameters such as forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF), a measure of

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expiratory muscle strength in patients without airway obstruction [14]. Maximum static airway pressures (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP]) are also measured frequently, particularly in early stages of the disease.

Although the assessment of pulmonary function decline in DMD is important in routine patient care, there is still limited knowledge about the correlation between these pulmonary function parameters, their reliability and sensitivity to change over time. Recent natural history data were reported in order to better understand the influence of age, glucocorticoid use and disease status on pulmonary function evolution in DMD. Emerging evidence from these data indicates that in patients with DMD (i) PEF and FVC expressed as percent of predicted (PEF%p, FVC%p) are well correlated [15], (ii) GC use delays the onset of pulmonary function loss, but once established, the rate of decline is comparable between GC-users and patients who are currently not using GCs [16–18], (iii) loss of FVC, FEV1 and PEF expressed as percent predicted follow a linear rate of decline from ~80% to ~30% [15,18,19] and (iv) the time of loss of ambulation is a predictor of pulmonary function loss [19]. Moreover, FVC%p, FEV1%p and PEF%p appear to follow a more predictable and reliable change with age than maximum static airway pressures (MIP%p, MEP%p) and peak cough flow (PCF) [15,16].

Here we report pulmonary function data from a well-defined DMD patient cohort (not using concomitant GC) prospectively enrolled in a randomized, placebo-controlled, phase 3 clinical trial (DELOS, Duchenne muscular dystrophy long-term idebenone study) which demonstrated that idebenone, a short-chain benzoquinone, significantly reduced the loss of pulmonary function over the 52-week study period [20–22]. We have now further analyzed cross sectional (baseline) data from all trial participants and longitudinal data from the placebo group of DELOS to determine the correlation between dynamic and static pulmonary function outcomes, their inter-correlation as well as correlation to upper limb function and the annual rate of change with the goal to provide a comprehensive characterization of pulmonary function in 10–18 year old patients with DMD who are not taking concomitant GCs and further expand our understanding of the natural course of pulmonary disease in DMD.

2. Patients and methods

2.1. Prospective data collection

Pulmonary function data were obtained from patients participating in DELOS, a prospectively planned, multi-center, phase 3 clinical trial evaluating the efficacy of idebenone 900 mg/day (Raxone®, Santhera Pharmaceuticals, Switzerland) compared to placebo [20]. Patients were enrolled between July 2009 and December 2012 in study centers located in Belgium, Germany, the Netherlands, Switzerland, France, Sweden, Austria, Italy, Spain and the USA. The trial and any changes to the protocol were approved by relevant national authorities and the institutional review boards or independent ethics committees in the countries of the participating centers and conducted in accordance with good clinical practice and the principles of the Declaration of Helsinki. Prior to any study-related procedure, written informed consent was obtained from all patients and/or parents or guardian. This study is registered with ClinicalTrials.gov, number NCT01027884, and the overall outcome was reported previously [20–22].

2.2. Patients

Patients aged 10–18 years with a documented and confirmed diagnosis of DMD were eligible for enrollment. Study participants had to have stopped taking glucocorticoids (GC) at least 12 months prior to enrollment and were not allowed to take GC during the 52-week study period. Furthermore, only patients who had reached the stage of pulmonary function decline, defined as PEF%p < 80% were enrolled. Based on their PEF%p at baseline, study participants were stratified into two subgroups (PEF%p <40% and 40–80%). Exclusion criteria included: (i) dependence on assisted ventilation (non-invasive nocturnal, daytime non-invasive or continuous invasive), (ii) documented DMD-related hypoventilation for which assisted ventilation is needed according to current standard of care guidelines (e.g. FVC%p < 30%) and (iii) inability to form a mouth seal to allow precise assessment of pulmonary function and mouth pressures. Patients with symptomatic heart failure (high probability of death within one year of baseline) and/or symptomatic ventricular arrhythmias were also excluded from the study. There were no selection criteria for ambulatory status or for any dystrophin mutation type. The intent-to-treat (ITT) population consisted of 64 patients; 33 patients were randomized to the placebo group.

2.3. Pulmonary function tests

Pulmonary function tests (PFT) were performed during hospital visits at screening, at baseline (within 6 weeks from screening) and at weeks 13, 26, 39 and 52. FVC, FEV1 and PEF were assessed using a Pneumotrac Spirometer 6800 (Vitalograph, UK). MIP and MEP were measured with a MicroRPM instrument (Medical Supply Store, Chorley, UK). All PFTs were performed with the aid of a qualified, trained and certified operator and in accordance with the American Thoracic Society/European Respiratory Society guidelines [23]. At each study visit the PFTs were to be carried out in the following sequence: PEF, FVC (which included FEV1), MIP and MEP. For each pulmonary function parameter, the highest value from a minimum of three and up to five consecutive maneuvers was used for analysis. All PFT parameters were normalized for height (derived from ulnar length [24,25]), weight, age and race using established conversion equations as shown in Supplementary material Table S1.

2.4. General disease status

The general disease status of patients was determined by their ambulatory status and upper limb function. For this, patients were counted as non-ambulatory if they were a non-ambulant wheelchair user at baseline. Upper limb function was assessed by the Brooke Upper Extremity scale [26], a 6-item scale where a higher score indicates a more severe functional impairment of the upper limbs (Supplementary material Fig. S1).