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Original article

Long-term outcomes of steroid therapy for Duchenne muscular dystrophy in Japan

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Abstract

Introduction: Corticosteroids are effective for improving motor function in patients with Duchenne muscular dystrophy (DMD), but there is no consensus on a regimen that balances efficacy and side effects.

Methods: Data from three groups of DMD patients were retrospectively analyzed: those treated with 0.75 mg/kg/day prednisolone every day (daily group, $n = 51$); those treated with 1 mg/kg/day prednisolone on alternate days (intermittent group, $n = 36$), and those not treated with steroids (nontreatment group, $n = 42$).

Results: Although the age of ambulation loss did not differ significantly among the groups, the hazard ratios for ambulation loss relative to the nontreatment group were 0.24 (95% confidence interval [CI]: 0.11–0.54) in the daily group and 0.34 (95% CI: 0.19–0.62) in the intermittent group. The percentage of predicted forced vital capacity increased until 9.6 years of age (to 94.1%) in the daily group, until 8.8 years of age (to 96.9%) in the intermittent group, and until 7.2 years of age (to 87.6%) in the nontreatment group. Weight gain was the most frequently observed side effect in the treated groups. Height was significantly lower in the daily than in the nontreatment group. Other side effects were observed, but no patient discontinued therapy. There were no marked differences in benefits and side effects between the two treated groups.

Discussion: This is the first assessment of long-term outcomes of different steroid therapy regimens in Japanese DMD patients. Benefits and side effects, except height, did not differ significantly between steroid regimens.

Keywords: Ambulation; Corticosteroid treatment; Height; Mixed model; Respiratory function; Side effect

1. Introduction

Duchenne muscular dystrophy (DMD) is a progressive muscular disorder caused by an X-linked recessive mutation in DMD, resulting in the loss of the muscle structural protein dystrophin, an unstable muscle fiber membrane, and impaired intracellular homeostasis [1,2]. Symptoms of DMD, including gait disturbance,

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frequent falls, and difficulty climbing stairs, usually appear between 2 and 5 years of age. Complete loss of ambulation (LOA) manifests by 12 years of age, and most patients die in their 30 s of cardiac and respiratory failure.

Steroid therapy was first reported effective for DMD patients in 1974 [3]. Later clinical trials confirmed that steroid therapy effectively prolonged muscle strength and ambulation in DMD patients [4], and the utility of steroid therapy for muscle weakness has been widely accepted [5–13]. Steroid therapy improves muscle strength within a period of weeks to months and extends patient ambulation, an important parameter for the activities of daily living (ADL), for up to 2–3 years. Although clinical trials of various other therapeutic approaches, including exon skipping and stop codon read-through, are now in the planning and implementation stages, data are available only on the ease of use and clinical effectiveness of steroid therapy. Guidelines for the use of corticosteroids in DMD were published by the American Academy of Neurology and the Child Neurology Society in 2005 and 2016 [14,15], respectively, there is at present no standardized perception or practice regarding the use of steroid therapy for DMD in Japan. This retrospective study therefore analyzed the effects of different steroid regimens on ADL in patients with DMD, with particular attention to ambulation, respiratory function, and side effects.

2. Patients and methods

2.1. Patients

The medical records of DMD patients who were followed up at the Department of Child Neurology, National Center Hospital, National Center of Neurology and Psychiatry (NCNP) were retrospectively analyzed. Of the 172 patients registered with the NCNP at the time of data analysis in October 2014, 43 were excluded because they received a nonstandard steroid treatment regimen or because patient data lacked essential information for statistical analysis (such as prednisolone dose, date of birth, or date of assessment). Longitudinal data on the remaining 129 patients were collected from 1987 to October 2014. The diagnosis of DMD was based on the results of muscle biopsy or genetic analysis by multiplex ligation-dependent probe amplification, a polymerase chain reaction method, and direct sequencing. Prior to treatment, the parents of each patient were informed about steroid-associated complications and treatment alternatives, and were subsequently offered the choice to initiate steroid treatment. Parents were also informed that deflazacort was not yet available in Japan. Although the standard prednisolone treatment regimen in Japan was 1 mg/kg/day on alternate days, the dose of prednisolone and the stage at which steroid therapy was initiated were at the discretion of each attending physician, based on assessments of declining muscle power. All patients were aged >5 years, received steroid therapy for >6 months before LOA, were ambulatory at their initial examination at our hospital, regularly attended follow-up appointments, and completed a live vaccine schedule at least 1 month before the initiation of steroid therapy.

Patients were divided into three groups according to prednisolone treatment regimen: patients treated with 0.75 mg/kg/day prednisolone every day (daily group) [14], patients treated with 1 mg/kg/day prednisolone on alternate days (intermittent group), and patients not treated with steroids (nontreatment group). As very few patients received other regimens, such as 0.5 or 0.75 mg/kg/day for 10 days "on" and 10–20 days "off," those patients were excluded from the final analysis.

2.2. Study protocol

Patients were followed-up at 1–6 month intervals. Each standard follow-up hospital visit included muscle function and neuromuscular tests, physical findings, and social and side effects, as recorded by attending physicians, nurses, physiotherapists, and occupational therapists. The respiratory function of each patient was measured 1–2 times per year. Respiratory management, including cough assist techniques, mechanical insufflation–exsufflation, and noninvasive/invasive ventilation, was similar for older patients in the 3 groups. Cardiac function and scoliosis were evaluated if necessary. Common side effects of steroid treatment, such as weight gain, short stature, behavioral changes, gastrointestinal complications, blood pressure changes, glucosuria, acne, and hirsutism, were documented. All study protocols were approved by the institutional review board of our institution, and the parent of each participant provided informed consent/assent prior to inclusion in the study.

2.3. Evaluations

Ambulation was defined as independent functional walking without a brace or any assistive device. The height of ambulatory patients was measured using a calibrated height meter; if a patient could not stand, height was measured in joint segments while the patient lay supine with the hip and knee joints straightened as much as possible, and the median of three measurements was recorded. Muscle function was evaluated by a physiotherapist. Respiratory function was measured 1–2 times per year using a spirometer (CHESTAC-11, 7700, 7800; Chest M.I., Inc., Japan), with the patient in a seated position and a 30 min recovery period between maneuvers. Percent predicted forced vital capacity (%FVC) was calculated as the percentage of predicted forced