

Original

## Long-term and Low-dose Steroid Therapy for Cardiomyopathy in Duchenne Muscular Dystrophy Patients

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Steroid therapy in Duchenne muscular dystrophy (DMD) patients slows motor function decline. Moreover, continued treatment slows respiratory failure and scoliosis progression. Cardiac function might also improve though data are as yet limited. Herein, we retrospectively evaluated the efficacy of our long-term, low-dose steroid regimen, at one-third the widely-used dose, for cardiomyopathy and respiratory dysfunction in our DMD patients. Clinical longitudinal data were available for 7 steroid-treated (15.7–24.7 y, median 24.3 y) and 10 non-steroid-treated (15.2–32.6 y, median 21 y) non-ambulant DMD patients over 15 years of age. The prednisolone (PSL) dose was 0.5 mg/kg every other day (0.25 mg/kg/day) and was continued after ambulation loss. Ages at ambulation loss, cardiomyopathy onset and the initiation of non-invasive ventilation (NIV) were analyzed. No apparent steroid side effects, except acne vulgaris, occurred. The two groups did not differ significantly in age at loss of ambulation. Five of 10 non-treated and one of 7 steroid-treated patients needed NIV, not a statistically significance difference. Nine of 10 non-steroid-treated but only two of 7 steroid-treated patients had cardiomyopathy, showing a statistically significant difference. Our results indicate that 0.25 mg/kg/day PSL, while not prolonging ambulation, does prevent cardiomyopathy progression with continuous use.

**Key Words:** Duchenne muscular dystrophy (DMD), steroid therapy, cardiomyopathy, loss of ambulation

### Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a gene mutation that results in a markedly reduced amount or complete absence of the cytoskeletal protein dystrophin<sup>1)</sup>. Affected boys develop proximal muscle weakness in early childhood, with loss of ambulation between ages 7 and 12<sup>2)3)</sup>. Progressive respiratory dysfunction typically emerges early in the second decade and these boys require noninvasive ventilation (NIV) in the mid to late teens. Scoliosis usually develops several years after they become fully wheelchair dependent. Cardiomyopathy commonly emerges in the second decade of life. Without intervention, death usually occurs in the late teens or twenties from respiratory or cardiac complications.

Steroids are the only medication currently available that stabilizes muscle strength and functions in DMD<sup>4)~7)</sup>, and that also reduces the risk of scoliosis and stabilizes pulmonary function<sup>8)9)</sup>. The mechanisms underlying the beneficial effects of steroid therapy in DMD are not known, though several hypotheses have been proposed. The clinical investigation of Duchenne dystrophy (CIDD) group showed a daily dose of 0.75 mg/kg to be the most effective therapy in their randomized, controlled trials, and this regimen has now become a standard protocol for patients, with DMD. The dose-response analysis showed that a lower dose of 0.3 mg/kg per day was not effective<sup>5)10)</sup>, although a higher dose of 1.5 mg/kg daily provided no additional benefit<sup>11)</sup>. Daily steroid use is more effective but has more side effects than alternate day treatment. While the

main goal of steroid therapy used to be the preservation of ambulation, many experts have recently opted to continue medication after the loss of ambulation, for the purpose of preserving upper limb strength, reducing progression of scoliosis, and stabilization of respiratory functions<sup>89</sup>. Several studies have suggested that steroid therapy can retard the progression of cardiac dysfunction in DMD<sup>12-15</sup>, however the efficacy of long-term steroid therapy for cardiomyopathy remains uncertain.

We have been studying the efficacy of long-term low-dose steroid therapy, at one-third the widely-used dose, for DMD patients. The main purpose of this regimen was long-term use with avoidance of the side effects of steroids. The dose was 0.5 mg/kg of prednisolone (PSL) every other day (0.25 mg/kg/day), less than the reported minimum effective dose. Herein, we retrospectively evaluated our low-dose steroid regimen for cardiomyopathy in DMD patients. We also evaluated the efficacy of this regimen for prolongation of ambulation and slowing respiratory dysfunction.

## Patients and Methods

### 1. Patients

Among 40 patients with DMD followed at the Department of Pediatrics, Tokyo Women's Medical University between January 2000 and December 2011, 7 steroid-treated and 10 non-steroid-treated patients who met the following criteria were included: ① ambulation had already been lost and current age was over 15 years ② echocardiographic studies had been performed at least every year since the age 12 years ③ complete medical records were available, and for the steroid-treated group ④ there had been at least 1 year of treatment ⑤ starting before loss of ambulation ⑥ with continuous use after the loss of ambulation. The diagnosis of DMD was based on the clinical phenotype and confirmation by lack dystrophin staining of muscle biopsy specimens and/or documentation of the dystrophin gene mutation.

The patients were given the option of steroid therapy when there was early clinical evidence of decreasing muscle function. The PSL dose was maintained at 0.5 mg/kg every other day (0.25 mg/

kg/day) and usually taken at breakfast. These patients were followed by the same multidisciplinary team and with the same clinical protocol.

### 2. Methods

The clinical data were reviewed retrospectively. The patients were assessed and followed by the same pediatric neurologists and cardiologists. Ages at ambulation loss, starting NIV and cardiomyopathy onset and were analyzed. NIV was initiated when the percent predicted value of forced vital capacity (FVC-PP) was <20% and/or nighttime monitoring of PCO<sub>2</sub> was >50 mmHg. Pulmonary function testing including FVC-PP was performed every 4 months at a minimum and nighttime monitoring of PCO<sub>2</sub> was carried out every 12 months after 12 years of age. All patients underwent a cardiac evaluation every 6–12 months, including BNP determination, electrocardiography and transthoracic echocardiography. Serial echocardiographic measures included left ventricular (LV) end-diastolic dimension, LV end-systolic dimension, left ventricular mass, and LV shortening fraction (SF). Pulse Doppler echocardiography was used to calculate left ventricular performance Tei index, as previously described<sup>16</sup>. Cardiomyopathy was defined by a LVSF <27% and/or LV Tei index >0.5<sup>17</sup>.

### 3. Statistical analysis

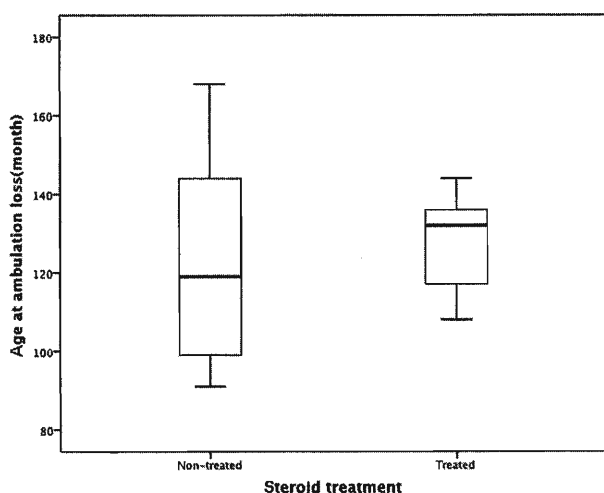
Data analysis was performed using the SPSS package (SPSS 2011, Statistics Version 20.0.0, SPSS Inc, Chicago, IL, USA). Fisher's exact test was used to compare the ratio of NIV initiation and cardiomyopathy in patients treated with or without steroids. The ages at loss of ambulation, NIV initiation and cardiomyopathy onset were analyzed by Mann-Whitney U test. The level of significance was set at 0.05.

### Results (Table)

Seven steroid-treated (15.7–24.7 y, median 24.3 y) and 10 non-steroid-treated (15.2–32.6 y, median 21 y) DMD patients were included in this study. The mean age at steroid therapy initiation was rather late (mean age: 8.6 ± 0.7 y). No significant steroid side effects, such as obesity, cushingoid appearance, or cataract, were seen in steroid treated-patients,

**Table** Comparison between steroid-treated and non-steroid-treated patients

	Steroid-treated N=7	Non-steroid-treated N=10	p value*
Median age (range) (years)	24.3 (15.7-24.7)	21 (15.2-32.6)	—
Age at steroid therapy initiation Mean $\pm$ SD (years)	8.6 $\pm$ 0.7	—	—
Age at ambulation loss Mean $\pm$ SD (years)	10.6 $\pm$ 1.2	9.6 $\pm$ 1.6	0.601
Ratio of NIV initiation	1 (14%)	5 (50%)	0.160
Ratio of Cardiomyopathy	2 (29%)	9 (90%)	0.018*

**Fig. 1** Ages at ambulation loss

The steroid-treated boys stopped walking after 9 years of age (mean age:  $10.6 \pm 1.2$  y), while the ages at loss of ambulation in the non-treated group were variable (mean age:  $9.6 \pm 1.6$  y). There was no statistically significant difference between the two groups ( $p = 0.601$ ).

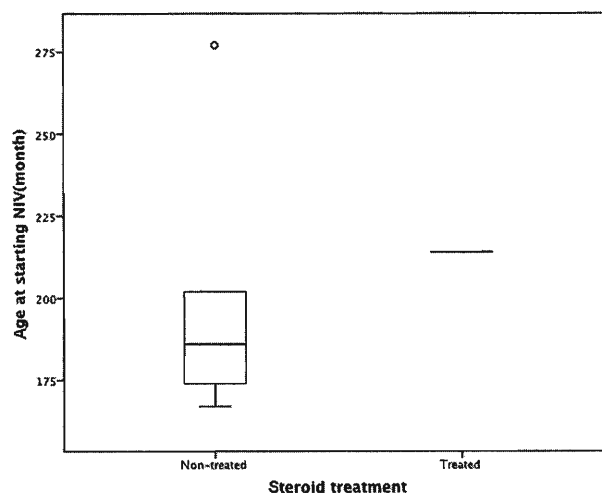
except acne vulgaris. No PSL dose reductions were necessitated by steroid side effects.

### 1. Ambulation period

The steroid-treated boys stopped walking after 9 years of age (mean age:  $10.6 \pm 1.2$  y). The ages at loss of ambulation in the non-treated group were variable and two patients had already lost the ability to walk by age 7 years (mean age:  $9.6 \pm 1.6$  y). There was no statistically significant difference in age at loss of ambulation between the two groups ( $p = 0.601$ ) (Fig. 1).

### 2. Respiratory dysfunction

Five of 10 non-treated patients (50%) needed NIV, four of them before the mid-teens. By contrast, only one of 7 steroid-treated patients (14%) needed NIV. Among those over age 20 years, four of 6 non-

**Fig. 2** Ages at starting NIV

Five of 10 non-treated patients needed NIV, four of them before the mid-teens.

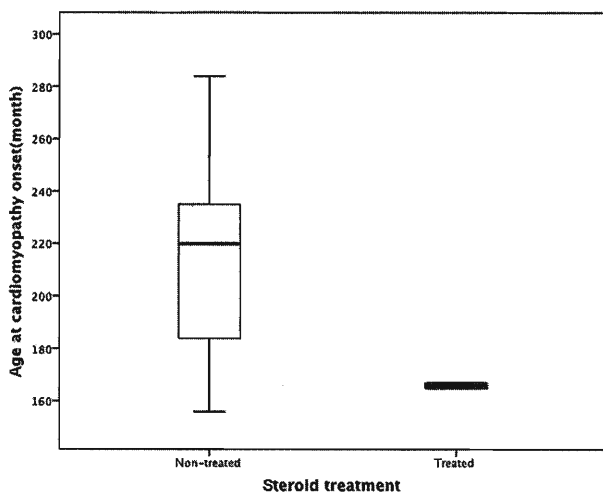
treated patients needed NIV, while only one of 5 steroid-treated patients started NIV. Respiratory decline tended to be slower in the steroid-treated patients, though the difference did not reach statistical significance ( $p = 0.160$ ,  $p = 0.175$  when limited to subjects over age 20 years) (Fig. 2).

### 3. Cardiomyopathy

Nine of 10 non-steroid-treated patients had cardiomyopathy (90%), while only two of 7 steroid-treated patients (29%) developed cardiomyopathy, clearly a statistically significant difference ( $p = 0.018$ ). However, the cardiomyopathy onset of two patients treated with steroids was before the mid-teens, rather earlier than in the non-treated group (Fig. 3).

### Discussion

Many different medications have been tried for patients with DMD, but only steroid therapy offers the benefit of preserving muscle function<sup>4)~7)</sup>. While



**Fig. 3** Ages at cardiomyopathy onset

Nine of 10 non-steroid-treated patients had cardiomyopathy, while only two of 7 steroid-treated patients developed cardiomyopathy. However, the cardiomyopathy onset of two patients treated with steroids was before the mid-teens, rather earlier than in the non-treated group.

early studies focused only on short-term improvement of muscle strength<sup>10,11</sup>, subsequent longer-term studies reported efficacy in prolonging ambulation. Thus, the goal and endpoint of steroid therapy has been set at the point when patients lose ambulation<sup>4-7</sup>. However, many experts continue medication after the loss of ambulation to preserve upper limb strength, reduce the risk of progressive scoliosis and stabilize respiratory function<sup>8,9</sup>.

Steroid therapy might have beneficial effects on cardiomyopathy in DMD patients. A few studies have indicated a slower decline in echocardiographic or magnetic resonance imaging measures<sup>12-15</sup>. In longer-term studies, steroid therapy appeared to reduce the prevalence of cardiomyopathy in DMD patients<sup>8,14</sup>. On the contrary, several side effects of steroid therapy are predicted to be injurious to cardiac function including cardiac hypertrophy, hypertension and hyperlipidemia. One report suggested steroids to cause deterioration of myocardial function in a dystrophin-deficient mouse model<sup>18</sup>. To date, the efficacy of steroids for cardiomyopathy in DMD patients remains unclear and data are limited.

Since the dose-response analysis showed that a lower dose of 0.3 mg/kg/day was not effective for

preserving muscle strength<sup>10</sup>, the standard dose of PSL has been set above 0.3 mg/kg per day and is usually 0.75 mg/kg/day. In our study as well, there was no significant difference in age at loss of ambulation between the two groups. This observation suggested that the dose of 0.25 mg/kg/day is not sufficient to preserve motor function.

There was a clear tendency for respiratory decline to be slower in the steroid-treated patients, though the difference did not reach statistical significance. In our study, especially among those over age 20 years, most non-treated patients needed NIV, while only a few steroid-treated patients had to start NIV. It is possible that a statistically significant difference will emerge with further accumulation of patients.

This study clearly showed a statistically significant difference for cardiomyopathy with nine of 10 non-steroid-treated but only two of 7 steroid-treated patients developing cardiomyopathy. Our results indicate that even a small dose of PSL (0.25 mg/kg/day) can prevent the progression of cardiomyopathy with long-term use. Since the mechanism by which steroids prevent cardiomyopathy progression in DMD patients is unknown, we could not draw any conclusions in this study as to whether the steroid effect on cardiomyopathy was direct or indirect based on the improvement of respiratory function. However, the onsets of both patients who developed cardiomyopathy in the steroid-treated group were at age 13 years, somewhat earlier than the average of the non-treated group. The possibility remains that steroids can cause cardiomyopathy at an early stage in some steroid-treated patients.

In summary, 0.25 mg/kg/day of PSL did not prolong ambulation as previously reported, but did tend to preserve respiratory function and clearly prevented the progression of cardiomyopathy with long-term use. At this dosage, there were no significant steroid side effects. We can propose low-dose steroid therapy at a dose of 0.25 mg/kg/day based on its beneficial effects on non-ambulant DMD patients without exerting major side effects. However, this study has limitations, since the patient group was small. We need to accumulate more the pa-

tients and conduct further evaluation to confirm these preliminary findings.

### Declarations

The authors declare no conflict of financial interest.

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## Duchenne 型筋ジストロフィーにおける心筋障害への長期少量ステロイド療法の効果

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Duchenne 型筋ジストロフィー (DMD) へのステロイド療法は、効果が証明されている唯一の治療である。歩行期間延長に加え、呼吸筋障害や心筋症の予防効果も近年報告されている。心筋障害への予防効果も期待されているが、検討は十分になされていない。我々は、DMD 患者に欧米の推奨量の 1/3 という少量投与を長期間行い、心筋障害への効果に関して後方視的に検討した。2000 年から 2011 年までに当科に通院した DMD 患者 40 名の内、15 歳以上の歩行不能例を対象とした。投与期間 1 年以内、投与開始時歩行不能例は除外し、さらに歩行機能喪失後もステロイド療法を継続し、12 歳以後定期的に循環器小児科医のフォローを受けている例に限定した結果、最終的にステロイド投与群 7 例 (15.7~24.7 歳, 中央値 24.3 歳), 非投与群 10 例 (15.2~32.6 歳, 中央値 21 歳) の検討となった。プレドニゾロン (PSL) は 0.5 mg/kg 隔日投与 (0.25 mg/kg/日) とした。2 群において歩行可能期間、非侵襲的換気療法 (NIV) 導入の有無、心筋障害の有無について統計学的解析を行った。歩行可能期間に関しては 2 群間で有意差を認めなかった。NIV 導入に関して有意差には至らなかったが、投与群では 7 例中 1 例、非投与群では 10 例中 5 例が NIV を必要とし、投与群の方が呼吸機能が保たれている傾向を認めた。心筋障害に関しては、非投与群の 10 例中 9 例に認めたのに対し、投与群では 7 例中 2 例に過ぎず、統計的有意差をもって、投与群の方が心筋障害発症が少なかった。一方で、投与群の心筋障害発症例は、2 例ともに年齢が 13 歳と、非投与群に比較して早期である傾向がみられた。長期少量ステロイド療法は歩行期間延長の効果はないが、心筋障害抑制に効果が認められた。