

# Treatment of Duchenne muscular dystrophy with ciclosporin A: a randomised, double-blind, placebo-controlled multicentre trial



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**Background** Duchenne muscular dystrophy is a rare X-linked progressive disease characterised by loss of ambulation at about age 10 years, with death in early adulthood due to respiratory and cardiac insufficiency. Steroids are effective at slowing the progression of muscle weakness; however, their use is limited by side-effects, prompting the search for alternatives. We assessed the effect of ciclosporin A as monotherapy and in combination with intermittent prednisone for the treatment of ambulant patients with this disorder.

**Methods** Our study was a parallel-group, placebo-controlled, double-blind, multicentre trial at trial sites of the German muscular dystrophy network, MD-NET, over 36 months. Ambulant patients with Duchenne muscular dystrophy who were aged 5 years or older were randomly assigned to receive either ciclosporin A (3.5–4.0 mg/kg per day) or matching placebo. Allocation was done centrally with computer-generated random numbers. Patients and investigators were masked to the allocated treatment. After 3 months of treatment, both groups were also given intermittent prednisone for a further 12 months (0.75 mg/kg, alternating 10 days on with 10 days off). All patients who received at least one dose of study drug or placebo were included in the primary analysis. The primary outcome measure was manual muscle strength measured on the Medical Research Council (MRC) scale. This trial is registered with the German clinical trial register DRKS, number DRKS00000445.

**Findings** 77 patients were randomly assigned to the ciclosporin A group and 76 to the placebo group; 73 patients on ciclosporin A and 73 on placebo received at least one dose and were available for efficacy analyses. 3 months of treatment with ciclosporin A alone did not show any significant improvement in primary outcome measures (mean change in the proportion of a possible total MRC score [%MRC] was  $-2.6$  [SD 6.0] for patients on ciclosporin A and  $-0.8$  [4.9] for patients on placebo; adjusted group difference estimate  $-0.88$ , 97.5% CI  $-2.6$  to  $0.9$ ;  $p=0.26$ ). The combination of ciclosporin A with intermittent steroids was not better than intermittent steroids alone over 12 months (mean change in %MRC was  $0.7$  [7.1] for patients on ciclosporin A and  $-0.3$  [7.9] for patients on placebo; adjusted group difference estimate  $-0.85$ ,  $-3.6$  to  $1.9$ ;  $p=0.48$ ). Numbers of adverse events (75 in patients on ciclosporin A and 74 on placebo) and serious adverse events (four with ciclosporin A and four with placebo) did not differ significantly between groups.

**Interpretation** Ciclosporin A alone or in combination with intermittent prednisone does not improve muscle strength or functional abilities in ambulant boys with Duchenne muscular dystrophy, but is safe and well tolerated.

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## Introduction

Duchenne muscular dystrophy (Online Mendelian Inheritance in Man number 310200) is an X-linked progressive disease affecting about one in 3500 male livebirths in human beings.<sup>1</sup> Although motor milestones can be mildly delayed, the diagnosis is often made at about age 4 years when proximal muscle weakness becomes more evident. The progressive nature of the disease leads to loss of ambulation in early teenage years with subsequent respiratory insufficiency and dilative cardiomyopathy in the second decade of life in most patients. Mean age at death was about 19 years before the use of non-invasive ventilation, but now more patients survive into adulthood. The only drugs that have been shown to slow the progression of muscle weakness are glucocorticoids

(0.75 mg/kg daily prednisone or 0.9 mg/kg daily deflazacort).<sup>2–5</sup> Uncontrolled studies also report the beneficial effects of glucocorticoids on the development of respiratory insufficiency, cardiomyopathy, and scoliosis.<sup>4</sup> The precise mechanism by which glucocorticoids increase strength in patients with Duchenne muscular dystrophy is unknown, but there is evidence that their anti-inflammatory and immunosuppressive effects might have an important role.<sup>6–8</sup> Although the short-term use of glucocorticoids has proven efficacy in this disorder, their long-term use is limited by side-effects including weight gain, osteoporosis, and behavioural changes. Therefore alternative regimens such as alternating 10 days on with 10 days off 0.75 mg/kg prednisone have been used; however, these regimens seem to be less effective.<sup>4,9</sup>

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Ciclosporin A is a lipophilic cyclic undecapeptide and one of the essential immunosuppressive drugs used in many immune and non-immune childhood diseases.<sup>10</sup> It was chosen for use in this trial rather than other immunosuppressive drugs because two open trials<sup>11,12</sup> reported that daily treatment with 5 mg/kg ciclosporin A enhanced voluntary and tetanic force in people with Duchenne muscular dystrophy. More recently, a positive treatment effect of low dose ciclosporin A was also confirmed in the *mdx* mouse model of the disorder.<sup>13</sup> The aim of our study was to assess the effect of ciclosporin A in the treatment of ambulant patients with Duchenne muscular dystrophy, both as a monotherapy and in combination with intermittent prednisone as a steroid-sparing treatment.

## Methods

### Patients

Patients were recruited into this double-blind, randomised, placebo-controlled multicentre study at sites of the German muscular dystrophy network MD-NET in Mainz, Göttingen, Neuss, Vienna, Freiburg, Essen, Kiel, Munich, Berlin, Dresden, and Basel during from January, 2004, to January, 2007. Inclusion criteria were a minimum age of 5 years; the ability to walk independently for at least 50 m; a diagnosis of Duchenne muscular dystrophy proven by clinical symptoms, a high serum creatine kinase titre, genetic testing, or muscle biopsy analysis; and the ability to participate in the assessment of primary and secondary outcome measures. Exclusion criteria were previous treatment with glucocorticoids, new or changed treatment with food supplements during 3 months before inclusion, treatment with clenbuterol or

other sympathomimetics 3 months before inclusion, participation in other clinical trials, and any contraindication for treatment with glucocorticoids or ciclosporin A.

The clinical trial was approved by regulatory authorities and ethics committees at each study site and done in accordance with good clinical practice guidelines. The objectives, study design, risks, and benefits of participation were explained to all participants, and written informed consent was obtained from patients and parents before enrolment.

### Randomisation and masking

After screening for eligibility, patients were randomly assigned at a 1:1 ratio to receive either ciclosporin A or placebo. A stratified block randomisation with a randomly varying length of four or six participants and stratification for trial site was used. Allocation was based on computer-generated random numbers and was done centrally via facsimile. A number was communicated to identify the study drug for each randomly assigned patient, and the drug was identically prepacked to maintain the masking for the patient and investigator. To maintain the masking for the study statistician, reading permission was withdrawn from the computer directory containing randomisation information and was reassigned after the database was locked.

### Procedures

A daily ciclosporin A dose of 3.5–4.0 mg/kg bodyweight was chosen because it has been successfully used as a corticosteroid-sparing agent for other paediatric indications and is associated with fewer side-effects than is 5 mg/kg bodyweight.<sup>10</sup> Ciclosporin A was given twice daily as capsules, or as an oral solution for patients unable to swallow the capsules. Bodyweight categories were used to achieve a daily ciclosporin A dose of between 3.5 mg/kg bodyweight and 4.0 mg/kg bodyweight. Capsules and liquid solution placebo preparations were identical in appearance, weight, and taste to the study drug. After 3 months of monotherapy with ciclosporin A or placebo, intermittent prednisone was added for all patients (0.75 mg/kg bodyweight daily, 10 days on alternating with 10 days off medication) and the combined treatment was continued for a further 12 months. All study medication was prepared and packed by Novartis Pharma AG (Basel, Switzerland) according to good manufacturing practice.

The primary outcome was manual muscle testing assessed with an extended version of the Medical Research Council (MRC) score.<sup>14–16</sup> The MRC score is a validated method to assess muscle strength in patients with Duchenne muscular dystrophy in 28 different muscle groups including neck, shoulder, elbow, wrist, hip, knee, and ankle in defined positions with an ordinal 11-point scale. It has been used as primary outcome measure in other controlled trials for Duchenne muscular dystrophy.<sup>2,3</sup>

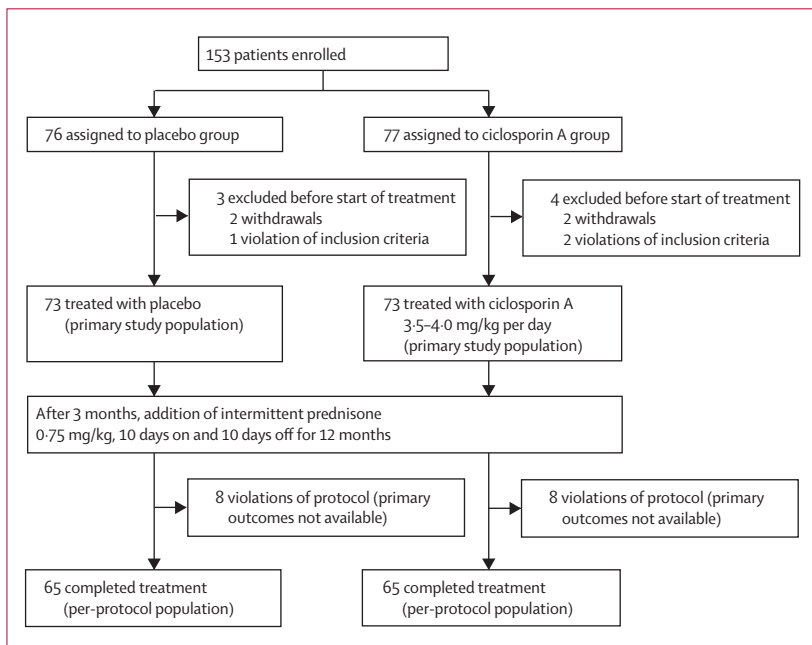


Figure 1: Trial profile

We calculated the MRC score as a proportion of a possible total score (%MRC), and used the change of %MRC between baseline and month 3 to assess ciclosporin A monotherapy. Subsequently, we used the change between month 3 and month 15 to assess the combination of ciclosporin A with intermittent prednisone. Additionally, quantitative muscle testing with Citec hand-held dynamometry (CIT Techniques, Haren, Netherlands) was used as a secondary outcome measure. The Citec dynamometer is a small hand-held device that is used to measure maximum isometric force in Newtons. Shoulder abduction, elbow flexion, hip flexion, knee extension, and ankle dorsiflexion were assessed on the patient's dominant side. According to a published protocol,<sup>17</sup> defined positions and locations for each muscle group were tested, and the best of three consecutive measurements was used for each muscle group. The total score for dynamometry measurement was calculated as the sum of the best value of each muscle group. For MRC and dynamometry scores, missing single items were replaced by mean values of the remaining items. The time to walk 10 m independently and the time to stand up from a supine position were used as functional outcome measures. Muscle strength assessment and timed tests were done by experienced physiotherapists at every site. A detailed manual and training material illustrating assessment of different muscle groups, and central training sessions for all evaluators before and during the trial on a yearly basis, were used to ensure the reliability of each rater and between each rater. The revised German KINDL questionnaire<sup>18</sup> was used as a generic quality of life measure for children. Primary and secondary outcome assessments were done at baseline and months 3, 9, and 15.

In parallel, the safety of ciclosporin A was monitored during and 30 days after discontinuation of the study drug by adverse event reports and monthly physical examination, assessment of blood pressure, and central laboratory tests (biochemistry and haematology). Because serum creatine titre is not a reliable biomarker for renal function in patients with Duchenne muscular dystrophy because of their low muscle mass, cystatin C was measured when the creatine titre increased. In the case of increased blood pressure or cystatin C titres above the normal range (0.55–1.15 mg/L), a dose reduction of ciclosporin A by a quarter was prescribed in the protocol. Additionally, an external investigator analysed ciclosporin A serum concentrations to detect potentially toxic titres and to lower the dose if appropriate. Random ciclosporin A serum titre alerts with consecutive dose reduction were done in the placebo group to maintain masking for the investigators.

### Statistical analysis

The sample size calculation was based on the primary endpoint (change in %MRC score). A normal distribution with an SD of four points was assumed, justified by previously published data.<sup>19–21</sup> Because two treatment

comparisons were done (one after each treatment section), a Bonferroni correction was applied—ie, two tests were planned at a two-sided significance level of 0.025 to control a type 1 error not exceeding 0.05. On the basis of the two-sample *t* test, the study was planned to detect a difference between the two treatment groups with a power of 80% if the true difference relates to an effect size of 0.5 (two points on the %MRC scale). Thus about 150 patients (75 per treatment group) were needed.

The primary analysis was done according to the intention-to-treat principle. Patients were further excluded from the primary analysis if no data for the primary endpoint were obtained, or one of two major objective inclusion criteria was violated (Duchenne muscular dystrophy diagnosis or ability to walk). To include patients with missing values, a last observation carried forward approach was used for %MRC and dynamometry. This approach corresponds to the assumption of constant development in muscle strength

	Placebo (n=73)	Ciclosporin A (n=73)	Total (n=146)
Age (years)	7.0 (1.4)	7.1 (1.5)	7.1 (1.5)
Weight (kg)	22.5 (4.8)	23.5 (6.0)	23.0 (5.5)
Height (cm)	118 (9)	119 (10)	119 (9)
Mental status*			
Average or above average for age	54 (74%)	52 (71%)	106 (73%)
Below average for age	19 (26%)	19 (26%)	38 (26%)
Physiotherapy before and during the trial			
Regular physiotherapy	60 (82%)	59 (81%)	119 (82%)
No regular physiotherapy	12 (16%)	13 (18%)	25 (17%)

Data are mean (SD) or number (proportion of available values). Differences in total numbers result from missing values. \*Mental status assessment was based on clinical judgment (n=116) or formal intelligence test (n=28).

**Table 1: Baseline characteristics of the primary study population**

	Placebo (n=73)	Ciclosporin A (n=73)	Adjusted group difference estimate* (97.5% CI); p value
<b>%MRC score</b>			
Baseline	59.8 (11.2)	62.7 (11.5)	..
Month 3	59.0 (11.0)	60.1 (10.8)	..
Change from baseline to month 3	-0.8 (4.9)	-2.6 (6.0)	-0.9 (-2.6 to 0.9); 0.26
Month 9	61.0 (12.4)	60.8 (12.7)	..
Month 15	59.6 (13.4)	59.8 (13.2)	..
Change from month 3 to month 15	0.7 (7.1)	-0.3 (7.9)	-0.9 (-3.6 to 1.9); 0.48
<b>Dynamometry sum score (Newtons)</b>			
Baseline	172.3 (68.9)	187.1 (72.3)	..
Month 3	172.8 (73)	187.4 (67.7)	..
Change from baseline to month 3	0.5 (38.0)	0.3 (30.9)	2.8 (-9.0 to 14.7); 0.59
Month 9	189.1 (77.9)	196.3 (78.8)	..
Months 15	182.4 (83.9)	207.0 (87.8)	..
Change from month 3 to month 15	9.6 (46.2)	19.6 (61.7)	11.4 (-8.7 to 31.5); 0.20

Data are mean (SD). %MRC=change in the proportion of a possible total Medical Research Council score. \*Group difference is ciclosporin A group minus placebo group (adjusted for age, baseline value, and trial site).

**Table 2: Effect of treatment on muscle strength as assessed by manual muscle testing and dynamometry**

measures for patients with missing data, whereas deterioration is expected to be realistic over the course of the study. We further assumed that study termination because of lack of efficacy in the placebo group has a higher probability than does termination owing to side-effects in the treatment group. Therefore, we judged this approach as conservative because it favours the placebo group.

Change in %MRC was analysed with a linear regression model with baseline value, treatment group, age, and trial site as covariates. As an additional post-hoc supportive analysis, a mixed regression model was set up for %MRC score to supply information about its development over time in the second phase (months 3–15), including month 9 data but without last observation carried forward replacement. The model contained age, trial site, treatment group, and time (months) from baseline of second phase (month 3) to time of measurement (month 9 and 15) for each treatment group separately (ie, time-by-treatment interaction). Subject was judged a random effect in the mixed regression model. For analysis of secondary outcome measures, no adjustment of  $\alpha$  values was used. Changes in dynamometry sum scores were analysed with the same linear regression model as described for %MRC scores.

Time-to-event endpoints were age at time of loss of ability to walk independently, age at time of loss of ability to rise unaided from a supine position, and time from random assignment to time of loss of ability to walk or rise. They were calculated as time from birth and random assignment until loss of ability to walk or rise. Patients still able to walk or rise were censored at the date of the last documented assessment. For group comparisons of time from random assignment to loss of ability to walk or rise, Kaplan-Meier estimation and log-rank tests were used. Additionally, Cox proportional hazards regression models were applied, incorporating age as a covariate. For age at loss of ability to walk or rise, Cox proportional hazards regression models accounting for left truncation were calculated. Results are presented as hazard ratios (HRs) with accompanying 95% CIs, describing the risk in the ciclosporin A group compared with the placebo group. In the analysis of timed functional tests, patients who had already lost the ability to do the test were integrated with an arbitrary large number (999 s representing infinity), and median values were used instead of means to incorporate data from these patients. Non-parametric methods (median, quartiles, IQR, and Wilcoxon tests) were then applied. For safety analysis, numbers of adverse events and other safety information (laboratory tests and blood pressure) were compared between groups.

Our study was registered in the Clinical Trials Register of the University Medical Centre Freiburg (number UKF000560). This registry was later integrated into the WHO-compliant German Clinical Trials Register (number DRKS00000445).

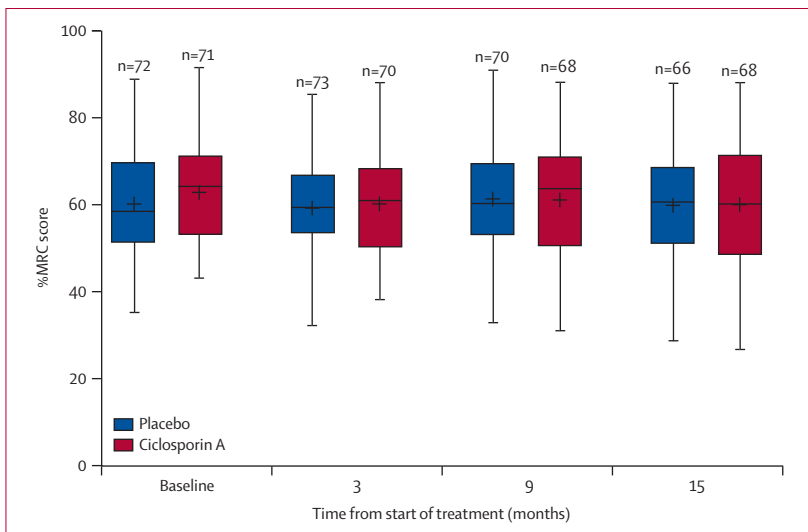
**Role of the funding source**

Novartis Pharma AG provided study medication and support in the management of serious adverse events. Neither Novartis Pharma AG nor the other funding sources had a role in the study design, data collection, data analysis, data interpretation, or the writing of the

	Placebo (n=73)	Ciclosporin A (n=73)	p value*
<b>Time to walk 10 m unaided (s)†</b>			
Baseline	6.5 (5.0 to 8.8); n=71	6.0 (5.1 to 8.0); n=72	..
Month 3	6.5 (5.4 to 9.2); n=73	6.2 (5.4 to 8.4); n=69	0.48
Change from baseline to month 3	0.3 (-0.3 to 1.1); n=71	0.3 (-0.2 to 1.0); n=68	0.57
Month 15	7.5 (5.0 to 11.1); n=66	6.1 (5.0 to 9.6); n=67	0.44
Change from month 3 to month 15	0.2 (-0.4 to 1.9); n=66	0.1 (-0.5 to 1.4); n=66	0.41
<b>Time to rise unaided from supine position (s)†</b>			
Baseline	7.8 (4.9 to 14.6); n=72	6.8 (4.6 to 12.0); n=72	..
Month 3	8.8 (5.6 to 22.1); n=73	7.7 (4.9 to 12.3); n=69	0.31
Change from baseline to month 3	0.8 (-0.1 to 4.2); n=72	0.3 (-0.4 to 3.1); n=68	0.35
Month 15	10.9 (4.8 to 36.2); n=63	7.4 (4.6 to 28.0); n=67	0.41
Change from month 3 to month 15	0.5 (-0.7 to 7.5); n=63	0.0 (-1.0 to 3.0); n=65	0.25
<b>Quality of life (KINDL questionnaire)‡</b>			
Baseline	93.9% (9.7); n=52	95.9% (7.7); n=51	..
Month 3	93.6% (9.2); n=57	95.3% (8.9); n=47	0.20
Change from baseline to month 3	-0.7% (8.2); n=46	-2.2% (8.7); n=38	0.77
Month 15	93.1% (9.9); n=43	93.7% (7.6); n=41	0.76
Change from month 3 to month 15	-0.5% (7.6); n=40	-2.9% (9.6); n=31	0.09

\*Wilcoxon two-sample test. †Data are median (IQR); number of observations. ‡Data are mean (SD); number of observations.

**Table 3: Effect of treatment on timed functional tests and quality of life**



**Figure 2: Boxplots of muscle strength assessed by manual muscle testing**

Boxes represent the IQRs, and whiskers indicate the minimum and maximum. The median is represented by the horizontal line at the middle of the box, and the cross represents the mean. Missing values of the primary study population have been replaced by last observation carried forward. n=number of real observations at each time point. %MRC=proportion of a possible total Medical Research Council score.

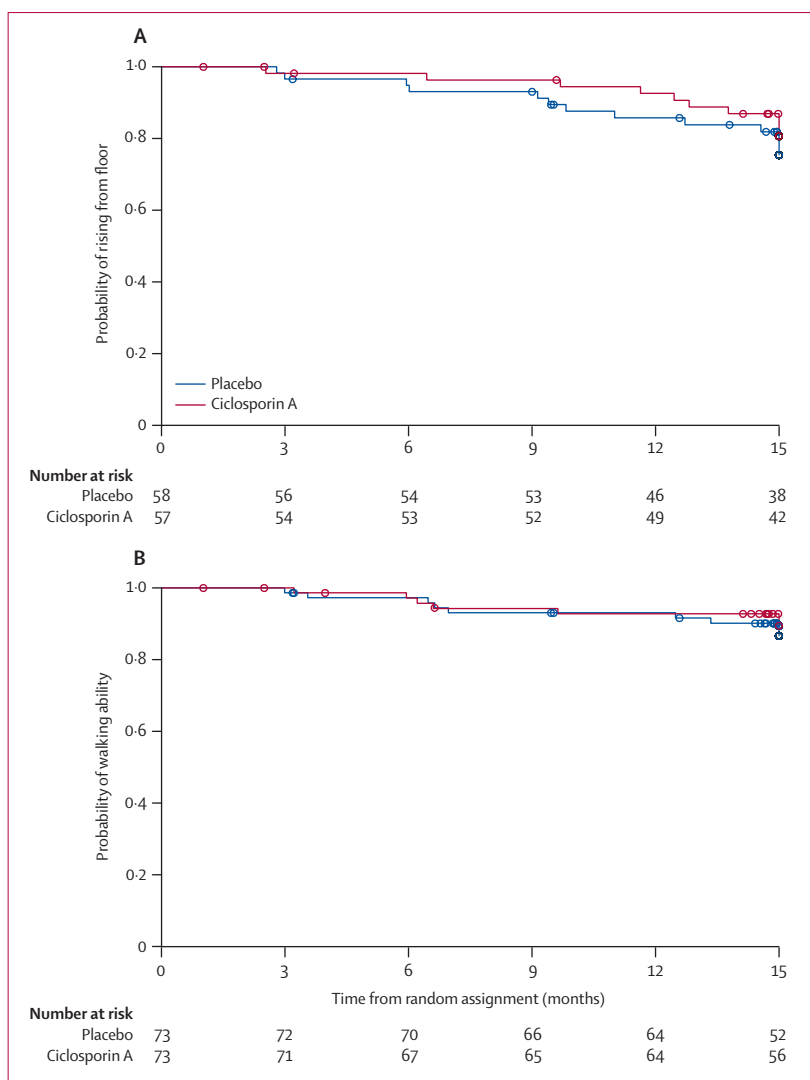
report. All authors had full access to all of the data and shared final responsibility for the decision to submit for publication.

## Results

Figure 1 shows the trial profile. After screening for eligibility, patients were randomly assigned over a recruitment period of 36 months to receive either ciclosporin A or placebo. After assignment seven patients were excluded because they were unable to walk independently at inclusion or withdrew from the trial before receiving any study medication. The remaining patients were included in the primary analysis (figure 1). Baseline characteristics were similar in both groups for age, cognitive function, muscle strength, functional abilities, and quality of life (tables 1–3).

Eight patients on placebo and eight on ciclosporin A did not complete the 15 months of treatment prescribed in the protocol. Of these patients, nine withdrew from the study early (six on placebo and three on ciclosporin A). The most common reasons for discontinuation were lack of therapeutic response (three on placebo and one on ciclosporin A) and non-compliance (three on placebo and one on ciclosporin A).

Muscle strength assessed by manual muscle testing (%MRC score) did not differ significantly between groups after 3 months of monotherapy with ciclosporin A or placebo or after an additional 12 months (month 15) of combined therapy with intermittent prednisone (table 2, figure 2). The mixed regression model for %MRC score in the second phase estimated the group difference for ciclosporin A compared with placebo at month 3 to be 0.7 (95% CI -2.4 to 3.7;  $p=0.67$ ), with an increase in the placebo group of 0.05 per month (-0.1 to 0.2;  $p=0.45$ ) and a decrease in the ciclosporin A group of -0.02 (-0.2 to 0.1;  $p=0.81$ );  $p$  for group difference in increase per month = 0.48). Secondary outcome measures including dynamometry, timed functional tests, or quality of life did not differ between the two groups (tables 2 and 3). Kaplan-Meier analysis for the loss of the ability to rise unaided from a supine to a standing position and for loss of the ability to walk 10 m unaided did not show any significant difference between groups (figure 3). At baseline, 31 patients (15 on placebo and 16 on ciclosporin A) were not able to rise unaided from the floor. During 15 months of treatment, 23 patients (13 on placebo and 10 on ciclosporin A) lost the ability to rise from the floor unaided and 16 patients (nine on placebo and seven on ciclosporin A) lost the ability to walk 10 m unaided. Cox regression adjusted for age at random assignment showed estimated HRs of the ciclosporin A group versus placebo of 0.75 (95% CI 0.28–2.00;  $p=0.56$ ) and 0.70 (0.30–1.59;  $p=0.39$ ) for time from random assignment to time of loss of the ability to walk and time to loss of the ability to rise, respectively. Similar results were recorded for the ages at which patients lost the ability to walk and rise (data not shown).



**Figure 3: Kaplan-Meier estimates**

(A) Time from random assignment to loss of ability to rise from the floor unaided (only patients still capable). (B) Loss of ability to walk 10 m. Circles denote censored values.

The number of adverse events did not differ between treatment regimens (74 on placebo and 75 on ciclosporin A). Four serious adverse events occurred in each group. All serious adverse events were classified as such because patients needed to be admitted to hospital owing to concomitant diseases. Serious adverse events in the ciclosporin A group were hyperglycaemia before the start of prednisone treatment, orthopaedic surgery, adenotomy, and work up for palpitation. In the placebo group, serious adverse events were orthopaedic surgery, adenotomy, viral upper respiratory tract infection, and surgery for inguinal hernia. None of these events was judged to be related to the study drug. The number of patients with abnormal blood pressure and abnormal laboratory values did not differ significantly between the groups (data not shown).

## Discussion

Findings from our study have shown that 3 months of daily treatment with 3·5–4·0 mg/kg ciclosporin A does not improve muscle strength compared with placebo in ambulant patients with Duchenne muscular dystrophy. Similarly, the addition of ciclosporin A to intermittent prednisone over a treatment period of 1 year does not show any significant difference in outcome from the placebo group. Our study was designed to detect an effect size of 0·5 (2 points on the %MRC scale) for the treatment group comparison with a power of 80%. A difference of two points on the %MRC scale relates to a change of 3·3% from baseline in our study population. Although we do not know exactly which change on the %MRC scale is clinically relevant, the upper limits of our CIs are both below 2 points and therefore probably do not include clinically relevant differences. In accordance with the results for muscle strength as assessed by manual muscle testing, we cannot show a significant effect for any of the secondary outcome measures, including dynamometry, ability and time to rise from a supine position, ability and time to walk 10 m unaided, and KINDL quality of life assessment. Treatment with ciclosporin A for 15 months was safe, with no significant difference in safety between the placebo and ciclosporin A groups.

Before the trial and after its completion, we systematically searched published work to identify additional evidence on the use of ciclosporin A in Duchenne muscular dystrophy (panel). Only one trial had assessment of the effect of the drug on muscle strength as its primary objective.<sup>11</sup> This was an open, uncontrolled trial showing improvement of muscle strength in a group of 15 patients after 8 weeks of treatment with 5 mg/kg ciclosporin A. All other trials used ciclosporin A in the setting of myoblast transfer experiments. Mendell and colleagues<sup>22</sup> randomly assigned 12 boys with Duchenne muscular dystrophy undergoing myoblast transfer to receive 5 mg/kg ciclosporin A or placebo and did not detect any significant difference between the groups. A year later, the researchers that had earlier studied monotherapy with ciclosporin A<sup>11</sup> did a myoblast transfer experiment in which ten patients received 5 mg/kg ciclosporin A. Although myoblast transfer was not effective, patients improved significantly and the improvement was attributed to the use of ciclosporin A.<sup>12</sup>

Our study does not confirm the results from the two open trials that suggested an increase in muscle strength after treatment with 5 mg/kg daily ciclosporin A.<sup>11,12</sup> Although the dose in these trials was higher than that in our trial, we do not recommend the use of higher doses of ciclosporin A in patients with Duchenne muscular dystrophy for two reasons. First, high doses of ciclosporin A inhibit the calcineurin signal transduction pathway, which is essential for successful regeneration of muscle tissue, and treatment of the *mdx* mouse model of Duchenne muscular dystrophy with high doses of

ciclosporin A led to deleterious effects on muscle morphology and a decrease in muscle strength.<sup>23</sup> Second, higher doses of ciclosporin A in people and especially children are associated with a substantially higher risk of renal and neural toxic effects and would thus greatly worsen the risk–benefit relation. Although a daily dose of 3·5–4·0 mg/kg ciclosporin A was well tolerated in our trial and others, about a quarter or more of patients show nephrotoxicity at daily doses of about 5 mg/kg.<sup>10</sup>

Why treatment with ciclosporin A does not benefit ambulant patients with Duchenne muscular dystrophy is open to speculation. The mode of action of ciclosporin A differs from that of glucocorticoids; its immunomodulatory action is mainly through the inhibition of effector T cells and suppression of lymphokine and interleukin production and release.<sup>10</sup> Effectiveness of glucocorticoids in the disorder might include other mechanisms such as stabilisation of muscle fibre membranes,<sup>24</sup> increase in myogenic repair,<sup>25</sup> or different regulation of genes in muscle fibres.<sup>26</sup> In the future, a more detailed understanding of the immunological mechanisms contributing to the pathogenesis of Duchenne muscular dystrophy might allow the design of more specific immunomodulatory therapies, such as blockade of tumour necrosis factor  $\alpha$ .<sup>8</sup> Additionally, the use of glucocorticoids needs further research to identify the medication and dose regimen with the best efficacy and acceptable side-effects.

In addition to the assessment of ciclosporin A, our trial provides information about the use of intermittent prednisone in Duchenne muscular dystrophy. Intermittent regimens have been suggested to lessen the adverse effects of long-term treatment with glucocorticoids, but evidence of their effectiveness is still scarce.<sup>4</sup> In a randomised, placebo-controlled, cross-over trial, Beenakker and colleagues<sup>9</sup> assessed 6 months of treatment with intermittent prednisone (0·75 mg, 10 days on and 20 days off) in 17 patients with Duchenne muscular dystrophy and reported an increase of muscle strength but no functional improvement during intermittent prednisone treatment. In our trial we noted stable %MRC scores and some improvement of myometry scores during 12 months of treatment with intermittent steroids, but a substantial number of patients lost functional abilities such as rising from the floor or walking unaided during the same period (figure 3). However, because there is no parallel control group for the use of intermittent prednisone in our trial, these data have to be interpreted with caution.

This is the largest placebo-controlled trial in Duchenne muscular dystrophy published so far. Although we found no evidence of a beneficial effect, we clearly show that meaningful randomised clinical trials with sufficient statistical power are possible even in rare diseases. As commercial interest and financial resources are often scarce, planning and doing such a trial needs the close cooperation of researchers, clinicians, patient groups,

**Panel: Research in context****Systematic review**

Before the trial and after its completion we applied a systematic search strategy to Medline, Embase, and the Cochrane Central Register of Controlled Trials with the terms “Duchenne muscular dystrophy” and “cyclosporin(e)” to identify additional evidence of the use of ciclosporin A in Duchenne muscular dystrophy. Only one uncontrolled trial had the primary objective to assess the effect of ciclosporin A on muscle strength in Duchenne muscular dystrophy.<sup>11</sup> Other trials used ciclosporin A in the context of myoblast transfer experiments.<sup>12,22</sup>

**Interpretation**

Our study does not confirm evidence from previous uncontrolled trials that ciclosporin A might improve muscle strength in patients with Duchenne muscular dystrophy. Furthermore, addition of ciclosporin A to an intermittent steroid regimen over 12 months did not seem to be beneficial for the treatment of ambulant patients.

public funding sources, and industry partners. The German network of muscular dystrophies MD-NET, which was founded in 2003 and has access to patients and a network of clinical trial sites, was therefore instrumental for this trial.

**Contributors**

RK, JK, JS, US, BR, and CS contributed to the design of the study. RK was the principal investigator and JK and JS were medical study coordinators. JK, JS, US, BR, GMS, EH, EW, GB, SW, FS, GW, WM-F, ST, UG, MvdH, JL, and RK participated in the study as investigators. GI wrote the statistical analysis plan of the protocol and analysed the data. JK, RK, JS, and GI wrote the first draft of the paper. All authors interpreted the data, contributed to the subsequent versions of the article, and approved the final report.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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