Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: a randomised trial


Summary

Background Most data for treatment of dermatomyositis and juvenile dermatomyositis are from anecdotal, non-randomised case series. We aimed to compare, in a randomised trial, the efficacy and safety of prednisone alone with that of prednisone plus either methotrexate or ciclosporin in children with new-onset juvenile dermatomyositis.

Methods We did a randomised trial at 54 centres in 22 countries. We enrolled patients aged 18 years or younger with new-onset juvenile dermatomyositis who had received no previous treatment and did not have cutaneous or gastrointestinal ulceration. We randomly allocated 139 patients via a computer-based system to prednisone alone or in combination with either ciclosporin or methotrexate. We did not mask patients or investigators to treatment assignments. Our primary outcomes were the proportion of patients achieving a juvenile dermatomyositis PRINTO 20 level of improvement (20% improvement in three of six core set variables at 6 months), time to clinical remission, and time to treatment failure. We compared the three treatment groups with the Kruskal-Wallis test and Friedman’s test, and we analysed survival with Kaplan-Meier curves and the log-rank test. Analysis was by intention to treat. Here, we present results after at least 2 years of treatment (induction and maintenance phases). This trial is registered with ClinicalTrials.gov, number NCT00323960.

Findings Between May 31, 2006, and Nov 12, 2010, 47 patients were randomly assigned prednisone alone, 46 were allocated prednisone plus ciclosporin, and 46 were randomised prednisone plus methotrexate. Median duration of follow-up was 35·5 months. At month 6, 24 (51%) of 47 patients assigned prednisone, 32 (70%) of 46 allocated prednisone plus ciclosporin, and 33 (72%) of 46 administered prednisone plus methotrexate achieved a juvenile dermatomyositis PRINTO 20 improvement (p=0·0228). Median time to clinical remission was 41·9 months in patients assigned prednisone plus methotrexate but was not observable in the other two treatment groups (2·45 fold [95% CI 1·2–5·0] increase with prednisone plus methotrexate; p=0·012). Median time to treatment failure was 16·7 months in patients assigned prednisone plus methotrexate but was not observable in the other two treatment groups (2·45 fold [95% CI 1·2–5·0] increase with prednisone plus methotrexate; p=0·012). Median time to treatment failure was 16·7 months in patients assigned prednisone plus methotrexate but was not observable in the other two treatment groups (2·45 fold [95% CI 1·2–5·0] increase with prednisone plus methotrexate; p=0·012). Median time to treatment failure was 16·7 months in patients assigned prednisone plus methotrexate but was not observable in the other two treatment groups (2·45 fold [95% CI 1·2–5·0] increase with prednisone plus methotrexate; p=0·012). Median time to treatment failure was 16·7 months in patients assigned prednisone plus methotrexate but was not observable in the other two treatment groups (2·45 fold [95% CI 1·2–5·0] increase with prednisone plus methotrexate; p=0·012). Median time to prednisone discontinuation was 35·8 months with prednisone alone compared with 29·4–29·7 months in the combination groups (p=0·009). A significantly greater proportion of patients assigned prednisone plus ciclosporin had adverse events, affecting the skin and subcutaneous tissues, gastrointestinal system, and general disorders. Infections and infestations were significantly increased in patients assigned prednisone plus ciclosporin and prednisone plus methotrexate. No patients died during the study.

Interpretation Combined treatment with prednisone and either ciclosporin or methotrexate was more effective than prednisone alone. The safety profile and steroid-sparing effect favoured the combination of prednisone plus methotrexate.

Funding Italian Agency of Drug Evaluation, Istituto Giannina Gaslini (Genoa, Italy), Myositis Association (USA).

Introduction

Juvenile dermatomyositis is a chronic disease that, similar to its adult equivalent, primarily affects skin and muscles. Despite improved disease outcomes with treatment strategies used over the past few decades, juvenile dermatomyositis is still associated with significant morbidity and mortality.14

Treatment of dermatomyositis for both children and adults is based on anecdotal evidence from case reports and retrospective studies, because very few randomised controlled trials have been done.2 Clinical consensus is that corticosteroids represent the first-line treatment of choice for juvenile dermatomyositis. In steroid-resistant or steroid-dependent cases, an immunosuppressive drug
is added as a steroid-sparing agent. The choice of the immunosuppressive agent relies mostly on the experience of the clinician and varies widely between countries.13,14

The two most common immunosuppressants used in the treatment of juvenile dermatomyositis are methotrexate and cyclosporin.15 However, a more aggressive therapeutic approach has been suggested, combining steroids and an immunosuppressive drug at disease onset, that could result in a better outcome.1,2 Yet, a Cochrane review16 has highlighted the paucity of randomised clinical trials, in both adults and children, assessing efficacy and safety of immunosuppressants in inflammatory myositis, concluding that evidence is inadequate to decide whether immunosuppressive agents are beneficial in dermatomyositis.

We did a randomised trial to establish whether, in patients with newly diagnosed juvenile dermatomyositis, combined treatment with prednisone and either methotrexate or cyclosporin has a safety and efficacy profile that is superior to prednisone monotherapy. Here, we present results after at least 2 years of treatment (induction and maintenance phases). The trial is ongoing in the extension phase (up to 5 years of treatment).

Methods

Patients

We did an international, multicentre, randomised, open-label, superiority trial at 54 centres in 22 countries that were part of the Paediatric Rheumatology International Trials Organisation (PRINTO).17 We enrolled children aged 18 years or younger with newly diagnosed and untreated probable or definite juvenile dermatomyositis, as per Bohan and Peter criteria (appendix p 4).11,12 We allowed previous treatment with prednisone if the daily dose was greater than 1 mg/kg for no more than 1 month. Major exclusion criteria were the presence of cutaneous or gastrointestinal ulceration or juvenile dermatomyositis-related pulmonary disease or cardiomyopathy.

Local ethics committees at every participating centre approved the study protocol. We obtained written informed consent or assent from every patient. Personnel at the PRINTO coordinating centre in Genoa, Italy,! verified patients’ inclusion and exclusion criteria, the primary outcome calculation of response, flare, inactivate disease, and corticosteroid tapering recommendations.

Randomisation and masking

We randomly allocated patients to either prednisone, prednisone plus cyclosporin, or prednisone plus methotrexate using SPSS version 19 to generate a progressive sequential list with no restriction. To conceal assignments, the randomisation list was accessible only by PRINTO personnel at the coordinating centre; participating investigators received the final allocation via email. Participants, clinicians (either the treating clinician or outcome assessors), and statisticians were not masked to group assignment.

Procedures

We divided our trial into three phases: induction (2 months), maintenance (22 months), and extension (at least 3 years; appendix p 17). The study database was locked after the last randomised patient had completed the induction and maintenance phases. At the beginning of the trial, we gave all children three daily pulses of intravenous methylprednisolone (30 mg/kg per pulse, for a maximum amount of 1 g per pulse) before randomisation to one of the three study groups. We administered cyclosporin at a dose of 4–5 mg/kg per day for at least 2 years in two oral doses. We gave methotrexate either subcutaneously or intramuscularly for at least 2 years at a dose of 15–20 mg/m² once a week plus either oral folic acid (1 mg/day except on the day of methotrexate administration) or folic acid (25–50% of the methotrexate dose in mg, the day after methotrexate administration), according to the attending clinician’s preference. In the induction phase, we gave all patients 2 mg/kg per day of prednisone or its equivalent in three daily doses (oral preferentially) for 1 month then tapered the dose by 0.25 mg/kg every week to reach a daily dose of 1 mg/kg per day at the end of month 2. We tapered the dose of prednisone gradually, as long as the patient remained clinically stable, to reach a daily dose of 0.2–0.5 mg/kg by the end of month 6, which was maintained until the end of month 12. Starting at month 13, we reduced the dose of prednisone to 0.1 mg/kg per day for a further 6 months then administered prednisone every other day until month 24. If a patient reached the status of inactive disease before month 24, prednisone could be discontinued. After the second year, treatment was at the discretion of the treating clinician. We did clinical assessments every month up to month 6, then every 3 months up to month 24, then every 6 months.

Outcomes

The primary short-term outcome (at 6 months) was the proportion of patients achieving the validated juvenile dermatomyositis PRINTO 20 level of improvement, which we defined as a 20% or greater improvement in three or more of the six variables of the juvenile dermatomyositis core set, with one or no variable worsening by more than 30% (muscle strength excluded).13–15 As secondary outcomes, we also assessed patients for higher levels of improvement—ie, juvenile dermatomyositis PRINTO 50, 70, and 90 levels of improvement. The six juvenile dermatomyositis core set variables, which have been validated by PRINTO, the American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR), are: muscle strength, assessed with the Childhood Myositis Assessment Scale (CMAS), with 0 the worst score and 52 the best; clinician’s global assessment of the patient’s
overall disease activity on a 0–10 cm visual analogue scale, with 0 the best score and 10 the worst, global disease activity assessment through the Disease Activity Score (DAS), with 0 the best score and 20 the worst, functional ability through the Childhood Health Assessment Questionnaire (C-HAQ), with 0 the best score and 3 the worst, and health-related quality of life (HRQL) through the parent version of the physical summary score of the Child Health Questionnaire (CHQ), with a low score indicating worse quality of life.

Primary long-term outcomes, measured after at least 2 years of treatment for the last randomised child, were: time to clinical remission, which we defined as clinically inactive disease persisting for at least 6 continuous months; time to clinically inactive disease, which we defined as normal muscle strength and clinician’s global assessment of disease activity equal to 0; time to treatment failure, which we defined as addition of ciclosporin or methotrexate, or any other disease-modifying antirheumatic drug, in any of the three study groups, or discontinuation of assigned treatment for any reason, including adverse events; and time to disease flare, which was defined in the protocol as at least 20% worsening from the previous assessment value in any two of the six juvenile dermatomyositis core set measures, with no more than one of the remaining variables improving by more than 30% (muscle strength excluded).

Main secondary outcome measures included time to prednisone discontinuation, change over time in individual juvenile dermatomyositis core set measures, and changes in serum muscle enzymes (creatine kinase, lactate dehydrogenase, aldolase, aspartate aminotransferase, and alanine aminotransferase), the results of which were standardised based on normal values provided by each local laboratory, as described elsewhere.

We assessed safety by recording adverse events and serious adverse events, which we recorded with the Medical Dictionary for Regulatory Activities (MedDRA) classification by system organ class and preferred term.

This study is registered with ClinicalTrials.gov, number NCT00323960.

**Statistical analysis**

We calculated that a sample size of 40 patients would be needed in each study group (total 120 patients) to have 80% power for comparison of combination treatments (prednisone plus methotrexate or prednisone plus ciclosporin) with the reference treatment (prednisone alone).

We summarised baseline characteristics and efficacy and safety variables with descriptive statistics. To assess proportions we used the $\chi^2$ test or Fisher’s exact test; for continuous variables we used the $t$ test or analysed data by ANOVA. We applied non-parametric ANOVA—the Kruskal-Wallis test to compare groups and Friedman’s test to compare repeated measures over time—in case of ordinal or non-normally distributed variables. For multiple hypothesis testing, we used Bonferroni’s correction (with $n=3$ posterior comparisons).

We calculated the treatment effect size of the mean values of continuous variables by dividing the mean difference by the standard deviation of the control group and expressed it as a mean difference in standardised mean difference (SMD) score indicating worse quality of life.

47 allocated prednisone

46 allocated prednisone plus ciclosporin

46 allocated prednisone plus methotrexate

47 analysed for primary outcome

46 analysed for primary outcome

46 analysed for primary outcome

Figure 1: Trial profile

<table>
<thead>
<tr>
<th>Prednisone (n=47)</th>
<th>Prednisone plus ciclosporin (n=46)</th>
<th>Prednisone plus methotrexate (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women 26 (55%)</td>
<td>26 (57%)</td>
<td>30 (65%)</td>
</tr>
<tr>
<td>Men 21 (45%)</td>
<td>20 (43%)</td>
<td>16 (35%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White European</td>
<td>32 (68%)</td>
<td>32 (70%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8 (17%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4%)</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (11%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>6.7 (4.6–10.0)</td>
<td>8.8 (5.0–11.3)</td>
</tr>
<tr>
<td>Age at first observation (years)</td>
<td>7.2 (5.1–10.1)</td>
<td>8.9 (5.3–12.4)</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>2.6 (1.2–5.1)</td>
<td>2.7 (1.2–6.2)</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>22.3 (17.5–31.3)</td>
<td>31.0 (18.0–41.7)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.9 (0.7–1.1)</td>
<td>1.1 (0.8–1.3)</td>
</tr>
<tr>
<td>Previous use of prednisone, or equivalent</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number of patients (%). No patients had previously received ciclosporin, methotrexate, or other drugs.
Between May 31, 2006, and Nov 12, 2010, 151 patients were screened for eligibility to our trial. 12 did not meet inclusion criteria; therefore, 139 were enrolled and randomly allocated to study treatment (figure 1). 47 patients were assigned prednisone alone, 46 were allocated prednisone plus ciclosporin, and 46 were randomised to prednisone plus methotrexate. Baseline characteristics are shown in table 1. No child had previously received ciclosporin or methotrexate. 67 children had treatment failures, the main reason being a major change in treatment: 19 children assigned to the prednisone group added methotrexate alone or in combination with other drugs; eight children in the prednisone plus ciclosporin group added methotrexate alone or in combination with other drugs; and nine children in the prednisone plus methotrexate either added intravenous immunoglobulin or ciclosporin or increased the corticosteroid dose.

At month 6, 24 (51%) of 47 patients allocated prednisone, 32 (70%) of 46 assigned prednisone plus ciclosporin, and absolute value of differences between values at the final visit and baseline by the SD of baseline values. For proportions, we calculated 95% CIs with the binomial exact method. We used the Kaplan-Meier method to produce survival curves and compared them with the log-rank test. We judged a p value less than 0.05 significant.

We calculated juvenile dermatomyositis PRINTO level of improvement with reference to the day of the first methylprednisolone intravenous pulse, whereas we based our calculation of disease flare on juvenile dermatomyositis core set variables at the previous visit in the subgroup of children who responded to at least 6 months of treatment. We regarded patients who withdrew early (eg, because of non-adherence to study drug administration, occurrence of an adverse event, or a major therapeutic change) as non-responders for all outcomes from that point onwards.

Our analysis was by intention to treat. We used Stata version 9.1 for descriptive and univariate analyses and Stata version 11.0 for calculation of binomial exact CIs and for survival analyses.

Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Italian Agency of Drug Evaluation reviewed the final report before submission. NR and AP had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 2: Juvenile dermatomyositis PRINTO levels of improvement at 6, 12, 18, and 24 months (short-term primary and secondary outcomes)

*Difference between prednisone alone and the two combination groups is significant.
33 (72%) of 46 randomised to prednisone plus methotrexate achieved a juvenile dermatomyositis PRINTO 20 improvement (p=0.0228; figure 2A). At month 24, juvenile dermatomyositis PRINTO 20, 50, or 70 improvements favoured a combination of prednisone plus either ciclosporin or methotrexate, versus prednisone alone (figures 2A, 2B, and 2C). A significant difference between study groups with respect to a juvenile dermatomyositis PRINTO 90 level of improvement was not seen at any point during the study (figure 2D).

The median duration of follow-up was 35·5 months (at least 2 years of follow-up for the last randomised child). The median time to clinical remission was 41·9 months in children allocated prednisone plus methotrexate, but patients allocated prednisone alone or prednisone plus ciclosporin had few remission events and median time to remission was not observable, with a 2·45 fold (95% CI 1·2–5·0) increase in clinical remissions with prednisone plus methotrexate (p=0.012; figure 3A). Clinical remissions were reported in eight patients assigned prednisone alone (incidence 6·0×1000 person-months), seven patients allocated prednisone plus ciclosporin (4·9×1000 person-months), and 15 patients randomised to prednisone plus methotrexate (13·4×1000 person-months). Time to clinically inactive disease was significantly earlier in the prednisone plus methotrexate group compared with the other study groups (p=0·021; appendix p 18).

The median time to treatment failure was 16·7 months with prednisone alone and 53·3 months with prednisone plus ciclosporin, but was not observable for prednisone plus methotrexate, with a 1·95 fold (95% CI 1·20–3·15) increase in treatment failures in the prednisone group (p=0·009; figure 3B). Treatment failures were reported in 30 patients assigned prednisone alone (incidence 30·5×1000 person-months), 20 patients allocated prednisone plus ciclosporin (17·5×1000 person-months), and 29 patients randomised to prednisone plus methotrexate (13·9×1000 person-months). Time to clinically inactive disease was not observable, with a 2·45 fold (95% CI 1·2–5·0) increase in clinical remissions with prednisone plus ciclosporin and prednisone plus methotrexate groups versus prednisone alone and 53·3 months with prednisone and prednisone + ciclosporin (13·9×1000 person-months).

Median time to disease flare did not differ between treatment groups (p=0·39; appendix p 19).

Median time to prednisone discontinuation was 35·8 months in the prednisone group, 29·4 months in the prednisone plus ciclosporin group, and 29·7 months in the prednisone plus methotrexate group, with a 1·65 fold (95% CI 1·24–2·14) increased chance of being corticosteroid free in the prednisone plus ciclosporin and prednisone plus methotrexate groups (p=0·002; figure 3C). Prednisone was discontinued in 19 patients assigned prednisone alone (incidence 15·9×1000 person-months), 31 patients allocated prednisone plus ciclosporin (27·8×1000 person-months), and 25 patients randomised to prednisone plus methotrexate (24·4×1000 person-months).

All three study groups showed a significant improvement over time in juvenile dermatomyositis core set measures and amounts of muscle enzymes (appendix p 19).
Adverse events are reported according to the Medical Dictionary for Regulatory Activities (MedDRA) classification by system organ class and preferred term. Only significant p values are reported. When safety events were repeated in time for the same patient, they were considered only once, “Combination of two or more preferred terms.”

Table 2: Adverse events

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Prednisone (n=47)</th>
<th>Prednisone plus ciclosporin (n=46)</th>
<th>Prednisone plus methotrexate (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>0 (0%)</td>
<td>3 (7%)</td>
<td>3 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (2%)</td>
<td>9 (20%)</td>
<td>2 (4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>0</td>
<td>3 (7%)</td>
<td>0</td>
<td>0.008</td>
</tr>
<tr>
<td>Weight increased</td>
<td>3 (6%)</td>
<td>1 (2%)</td>
<td>3 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>3 (7%)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Cushing's syndrome</td>
<td>0</td>
<td>5 (11%)</td>
<td>4 (9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dermo-hypodermitis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>9 (19%)</td>
<td>24 (52%)</td>
<td>9 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>10 (21%)</td>
<td>27 (59%)</td>
<td>9 (20%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue conditions</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>2 (4%)</td>
<td>5 (11%)</td>
<td>4 (9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>9 (19%)</td>
<td>6 (13%)</td>
<td>9 (20%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5 (11%)</td>
<td>14 (30%)</td>
<td>14 (30%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Abdominal pain or upper abdominal pain</td>
<td>2 (4%)</td>
<td>7 (15%)</td>
<td>0</td>
<td>0.008</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (6%)</td>
<td>4 (9%)</td>
<td>4 (9%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>5 (11%)</td>
<td>8 (17%)</td>
<td>1 (2%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (2%)</td>
<td>4 (9%)</td>
<td>2 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>1 (2%)</td>
<td>11 (24%)</td>
<td>1 (2%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (11%)</td>
<td>13 (28%)</td>
<td>13 (28%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>-</td>
<td>-</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (11%)</td>
<td>14 (30%)</td>
<td>14 (30%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Any drug intolerance</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Discussion

Our findings suggest that combination treatment with prednisone plus methotrexate is superior to prednisone alone when time to treatment drug discontinuation is defined in the prednisone plus methotrexate group (13 months in the prednisone monotherapy group). In the prednisone plus ciclosporin group, drug discontinuation was noted in the prednisone group (hyperemia, 13 in ten patients; prednisone group) by 12 months (after 12 months of treatment). Both time to clinical remission (40 months and after at least 6 continuous months) and time to clinical remission (40 months and after at least 12 months of treatment) are noted in the prednisone group. Therefore, in the prednisone plus ciclosporin group, 11 (in ten patients) were recorded in the prednisone group (40 months and after at least 12 months of treatment). In the prednisone plus methotrexate group, 11 (in ten patients) were recorded in the prednisone group (40 months and after at least 12 months of treatment).
failure was considered. Time to prednisone discontinuation also favoured the combination of prednisone with either ciclosporin or methotrexate over treatment with prednisone alone, which is an important finding because many children suffer from the side-effects of corticosteroids (panel).

It is difficult to compare our findings with those of other studies of both juvenile and adult dermatomyositis because available data are from, primarily, case series or non-randomised studies.\(^5\) Rituximab has been studied in a randomised, double-blind, placebo-phase trial in adult and paediatric patients with idiopathic inflammatory myopathies resistant to previous treatments, but the trial had negative results.\(^26\) Ramanan and colleagues\(^26\) compared a cohort of 31 children with juvenile dermatomyositis treated with prednisone plus methotrexate with a historical control of 22 patients with juvenile dermatomyositis who received prednisone alone. The cumulative prednisone dose in the group treated with the combination of prednisone and methotrexate was roughly half that recorded in the historical control group.

In our safety analysis, which included all randomised children, patients allocated prednisone plus ciclosporin had a greater number of adverse events when compared with those assigned prednisone alone or prednisone plus methotrexate. Similarly, the frequency of adverse events affecting skin and subcutaneous tissues or gastrointestinal and general disorders was significantly increased in the prednisone plus ciclosporin group compared with the prednisone alone or prednisone plus methotrexate groups. Infections were more frequent with combination treatment than with prednisone alone. The higher frequency of calcinosis in children treated with prednisone plus methotrexate should be interpreted with caution in view of the short length of follow up.

A limitation of our trial is that our sample did not allow for direct statistical comparison between the two combination treatments, even if findings of the safety analysis seemed to favour prednisone plus methotrexate over prednisone plus ciclosporin. Furthermore, masking was not implemented in our trial for ethical, logistical (double-blind dummy design), and economic reasons, because our study was in patients with a chronic disorder, undertaken by academic researchers, and supported by public bodies, with no support from pharmaceutical companies. Moreover, assessors at each of the participating centres were not masked to assignments, but the primary outcome measures used were the result of previous validation work in an independent dataset by the PRINTO network.\(^14\)–\(^15\)

In conclusion, our study suggests that combined treatment with prednisone and either ciclosporin or methotrexate at disease onset is more effective than prednisone alone. The safety profile and steroid-sparing effect favoured the combination of prednisone plus methotrexate. Prednisone plus methotrexate will possibly become the reference standard treatment with which to assess the efficacy and safety profile of new drugs for juvenile dermatomyositis. Furthermore, this combination could become the reference treatment in everyday clinical practice for paediatricians. New agents are needed to control disease activity and damage to children who do not respond or are resistant to standard combination therapy with prednisone plus methotrexate.

Panel: Research in context

**Background**

Juvenile dermatomyositis is a chronic disease that, similar to its adult equivalent, primarily affects skin and muscles. A recent Cochrane review has highlighted the paucity of randomised clinical trials assessing the efficacy and safety of immunosuppressants in inflammatory myositis for both children and adults. We designed a randomised trial to test the hypothesis that early introduction of combination treatment with prednisone and either ciclosporin or methotrexate could prove more effective and safer than prednisone alone for treatment of newly diagnosed juvenile dermatomyositis. Members of the Paediatric Rheumatology International Trials Organisation (PRINTO) undertook the trial, using disease activity core set measures validated by PRINTO, the American College of Rheumatology, and the European League Against Rheumatism.

**Interpretation**

139 children with juvenile dermatomyositis were randomly allocated either prednisone alone or prednisone in combination with ciclosporin or methotrexate. Median time to clinical remission, time to treatment failure, and time to discontinuation of steroids were superior with combination treatment compared with prednisone monotherapy. The frequency of adverse events was increased with prednisone plus ciclosporin, and the incidence of infections and infestations was significantly higher with both combination treatments. The safety profile and the steroid-sparing effect reported in this randomised trial favoured the combination of prednisone plus methotrexate.
work; grants from Novartis, Pfizer, AbbVie, Abbott, and Roche outside the submitted work; and personal fees from Novartis outside the submitted work. AGB-M reports other financial relationships with UCB outside the submitted work. MTg reports grants from Istituto Giannina Gaslini during the conduct of the study; grants and non-financial support from Pfizer outside the submitted work; grants, personal fees, and non-financial support from Novartis outside the submitted work; and personal fees and non-financial support from Roche and AbbVie outside the submitted work. AMA reports grants from AIFA during the conduct of the study; grants from Abbott, Bristol-Myers Squibb, Francesco Angelini, GlaxoSmithKline, Hoffman-La Roche, Italfarmaco, Janssen, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Sobi, Xoma, and Wyeth outside the submitted work; and other financial relationships with Abbott, Bristol-Myers Squibb, Astellas, Boehringer, Italfarmaco, MedImmune, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Roche, and Servier outside the submitted work. SO, FZ, Janssen, Novartis, Pfizer, and Servier outside the submitted work; grants and non-financial support from Abbott, Bristol-Myers Squibb, Astellas, Boehringer, MedImmune, Novartis, Novo Nordisk, Pfizer, and Servier outside the submitted work. SO, FZ, Janssen, Novartis, Pfizer, and Servier outside the submitted work; grants and non-financial support from Abbott, Bristol-Myers Squibb, Astellas, Boehringer, MedImmune, Novartis, Novo Nordisk, Pfizer, and Servier outside the submitted work.

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