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

Nicolino Ruperto, Angela Pistorio, Sheila Oliveira*, Francesco Zulian, Ruben Cuttica, Angelo Ravelli, Michel Fischbach, Bo Magnusson, Gary Sterba, Tadej Avcin, Karine Brochard, Fabrizia Corona, Frank Dressler, Valeria Gerloni, Maria T Apaz, Claudia Bracaglia, Adriana Cespedes-Cruz, Rolando Cimaz, Gerard Couillault, Rik Joos, Pierre Quartier, Ricardo Russo, Marc Tardieu, Nico Wulffraat, Blanca Bica, Pavla Dolezalova, Virginia Ferriani, Berit Flato, Ana G Bernard-Medina, Troels Herlin, Maria Trachana, Antonella Meini, Emma Allain-Launay, Clarissa Pilkington, Veronika Vargova, Carine Wouters, Simona Angioloni, Alberto Martini, for the Paediatric Rheumatology International Trials Organisation (PRINTO)†*

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 allocated prednisone, 53·3 months in those assigned prednisone plus ciclosporin, but was not observable in patients randomised to prednisone plus methotrexate (1·95 fold [95% CI 1·20–3·15] increase with prednisone; p=0·009). Median time to prednisone discontinuation was 35·8 months with prednisone alone compared with 29·4–29·7 months in the combination groups (p=0·002). 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.[1–3]

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.[4] 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

Published Online
November 29, 2015
http://dx.doi.org/10.1016/S0140-6736(15)01021-1

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(15)01023-5

*Contributed equally

†For a full list of investigators, see appendix (pp 1–3)

Istituto Giannina Gaslini, Pediatria II, Reumatologia, PRINTO Coordinating Centre, Genoa, Italy (N Ruperto MD, A Ravelli MD, S Angioloni BSA, A Martini MD); **Istituto Giannina Gaslini, Epidemiologia, Biostatistica e Comitati, Genoa, Italy** (A Pistorio MD); **Instituto de Puericultura e Pediatria Martagao Gesteira, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil** (S Oliveira MD); **Clinica Pediatrica I, Unità di Reumatologia Pediatrica, Padua, Italy** (F Zulian MD); **Hospital General de Ninos Pedro de Elizalde, Rheumatology Section, Buenos Aires, Argentina** (R Cuttica MD); **Università di Genova, Dipartimento di Pediatria, Genoa, Italy** (A Ravelli, A Martini); **Hôpital Universitaire Hautepierre, Pédiatrie I, Strasbourg, France** (M Fischbach MD); **Pediatric Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden** (B Magnusson MD); **Hospital de Clinicas Caracas, Caracas, Venezuela** (G Sterba MD); **University Children's Hospital, University Medical Centre Ljubljana, Department of Allergology, Rheumatology and Clinical Immunology, Ljubljana, Slovenia** (T Avcin MD); **Paediatric**

Nephrology and Internist Medicine, Hôpital des Enfants, Toulouse, France (K Brochard MD); Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Clinica Pediatrica II De Marchi, Milan, Italy (F Corona MD); Medizinische Hochschule Hannover, Kinderklinik, Hannover, Germany (F Dressler MD); Istituto Gaetano Pini, Divisione di Reumatologia, Milan, Italy (V Gerloni MD); Clínica Universitaria Privada Reina Fabiola, Universidad Católica de Córdoba, Rheumatology, Cordoba, Argentina (M T Apaz MD); Ospedale Pediatrico Bambino Gesù, Reumatologia, Rome, Italy (C Bracaglia MD); Centro Medico Nacional La Raza, Reumatologia Pediatrica, Mexico City, Mexico (A Cespedes-Cruz MD); Azienda Ospedaliero-Universitaria Meyer, Florence, Italy (R Cimaz MD); Hopital d'Enfants, Dijon, France (G Couillault MD); Universitair Ziekenhuis Gent, Centrum Voor Kinderreumatologie, Gent, Belgium (R Joos MD); Unité d'Immunologie, Hématologie et Rhumatologie Pediatrique, Université Paris-Descartes, IMAGINE Institute, Hôpital Necker-Enfants Malades, Paris, France (P Quartier MD); Hospital de Pediatria Juan P Garrahan, Servicio de Inmunología/Reumatología, Buenos Aires, Argentina (R Russo MD); Assistance Publique Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud and Université Paris Sud, Paris, France (M Tardieu MD); Department of Pediatric Immunology and Rheumatology, Wilhelmina Kinderziekenhuis, Utrecht, Netherlands (N Wulffraat MD); Hospital Universitário Clementino Fraga Filho, UFRJ, Clinica Medica, Reumatologia, Rio de Janeiro, Brazil (B Bica MD); Pediatric Rheumatology Unit, Charles University and General University Hospital, Department of Pediatrics and Adolescent Medicine, Prague, Czech Republic (P Dolezalova MD); Hospital das Clinicas da Faculdade de Medicina de Ribeirao Preto da Universidade de Sao Paulo, Department of Pediatrics, Division of Immunology, Allergy and Rheumatology, Ribeirao Preto, Brazil (V Ferriani MD);

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.[5,6]

The two most common immunosuppressants used in the treatment of juvenile dermatomyositis are methotrexate and ciclosporin.[5,6] 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.[7–9] Yet, a Cochrane review[4] 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 ciclosporin 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).[10] 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, inactive disease, and corticosteroid tapering recommendations.

Randomisation and masking

We randomly allocated patients to either prednisone, prednisone plus ciclosporin, 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 ciclosporin 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 folinic 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 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;[16] 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;[17] global disease activity assessment through the Disease Activity Score (DAS), with 0 the best score and 20 the worst;[18] functional ability through the Childhood Health Assessment Questionnaire (C-HAQ), with 0 the best score and 3 the worst;[19,20] parent's global assessment of the child's overall wellbeing on a 10 cm visual analogue scale, with 0 representing very good well-being and 10 being very poor wellbeing;[17,19,20] and health-related quality of life (HRQL) through the parent version of the physical summary score of the Child Health Questionnaire (CHQ),[20,21] 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;[22] 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.[23–26]

We assessed safety by recording adverse events and serious adverse events, which we recoded 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 χ^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 three 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

Oslo University Hospital, Rikshospitalet, Department of Rheumatology, Oslo, Norway (B Flato MD); **Hospital Civil de Guadalajara Fray Antonio Alcalde, Servicio de Reumatología, Guadalajara Jalisco, Mexico** (A G Bernard-Medina MD); **Skejby**

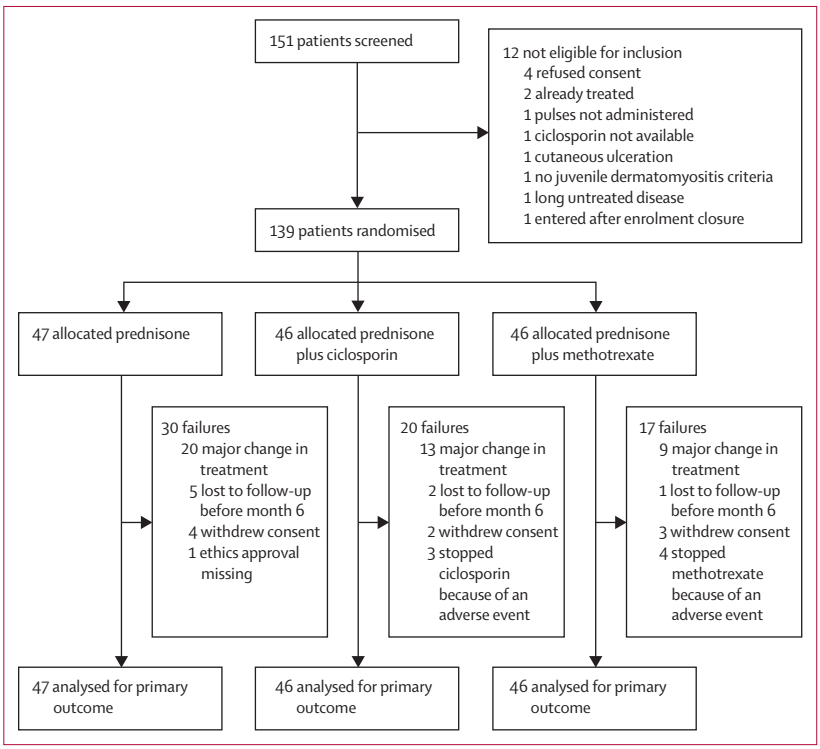

Figure 1: **Trial profile**

	Prednisone (n=47)	Prednisone plus ciclosporin (n=46)	Prednisone plus methotrexate (n=46)
Women	26 (55%)	26 (57%)	30 (65%)
Men	21 (45%)	20 (43%)	16 (35%)
Ethnic origin			
White European	32 (68%)	32 (70%)	29 (63%)
Hispanic	8 (17%)	5 (11%)	6 (13%)
Other	2 (4%)	5 (11%)	6 (13%)
Unknown	5 (11%)	4 (9%)	5 (11%)
Age at onset (years)	6·7 (4·6–10·0)	8·8 (5·0–11·3)	6·7 (3·9–10·1)
Age at first observation (years)	7·2 (5·1–10·1)	8·9 (5·1–12·4)	7·1 (4·3–10·4)
Disease duration (months)	2·6 (1·2–5·1)	2·7 (1·2–6·2)	2·8 (1·9–5·0)
Bodyweight (kg)	23·2 (17·5–31·3)	31·0 (18·0–41·7)	24·3 (17·0–38·0)
Body surface area (m^2)	0·9 (0·7–1·1)	1·1 (0·8–1·3)	0·9 (0·7–1·2)
Previous use of prednisone, or equivalent	3 (6%)	2 (4%)	3 (7%)

Data are median (IQR) or number of patients (%). No patients had previously received ciclosporin, methotrexate, or other drugs.

Table 1: **Baseline demographic and disease characteristics**

Sygehus, Aarhus University Hospital, Department of Pediatrics, Aarhus, Denmark (T Herlin MD); **Aristotle University of Thessaloniki, Ippokration General Hospital, First Department of Pediatrics, Ippokration Hospital, Thessaloniki, Greece** (M Trachana MD); **Clinica Pediatrica dell'Università di Brescia, Spedali Civili, Unità di Immunologia e Reumatologia Pediatrica, Brescia, Italy** (A Meini MD); **CHU Clinique Médicale Pédiatrique, Nantes, France** (E Allain-Launay MD); **Great Ormond Street Hospital for Sick Children, Centre of Paediatric and Adolescent Rheumatology, University College London, London, UK** (C Pilkington MD); **Detska Fakultna Nemocnica, First Pediatric Department, Kosice, Slovakia** (V Vargova MD); **and University Hospital Gasthuisberg, Department of Pediatrics, Division of Pediatric Rheumatology, Leuven, Belgium** (C Wouters MD)

Correspondence to:
Dr Nicolino Ruperto, Istituto Giannina Gaslini, Paediatric Rheumatology International Trials Organisation (PRINTO), EULAR Centre of Excellence in Rheumatology 2008–2013, Pediatria II, Reumatologia, 16147 Genoa, Italy
nicolaruperto@gaslini.org

See Online for appendix

For more on **PRINTO** see http://www.printo.it

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 Statistica 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

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

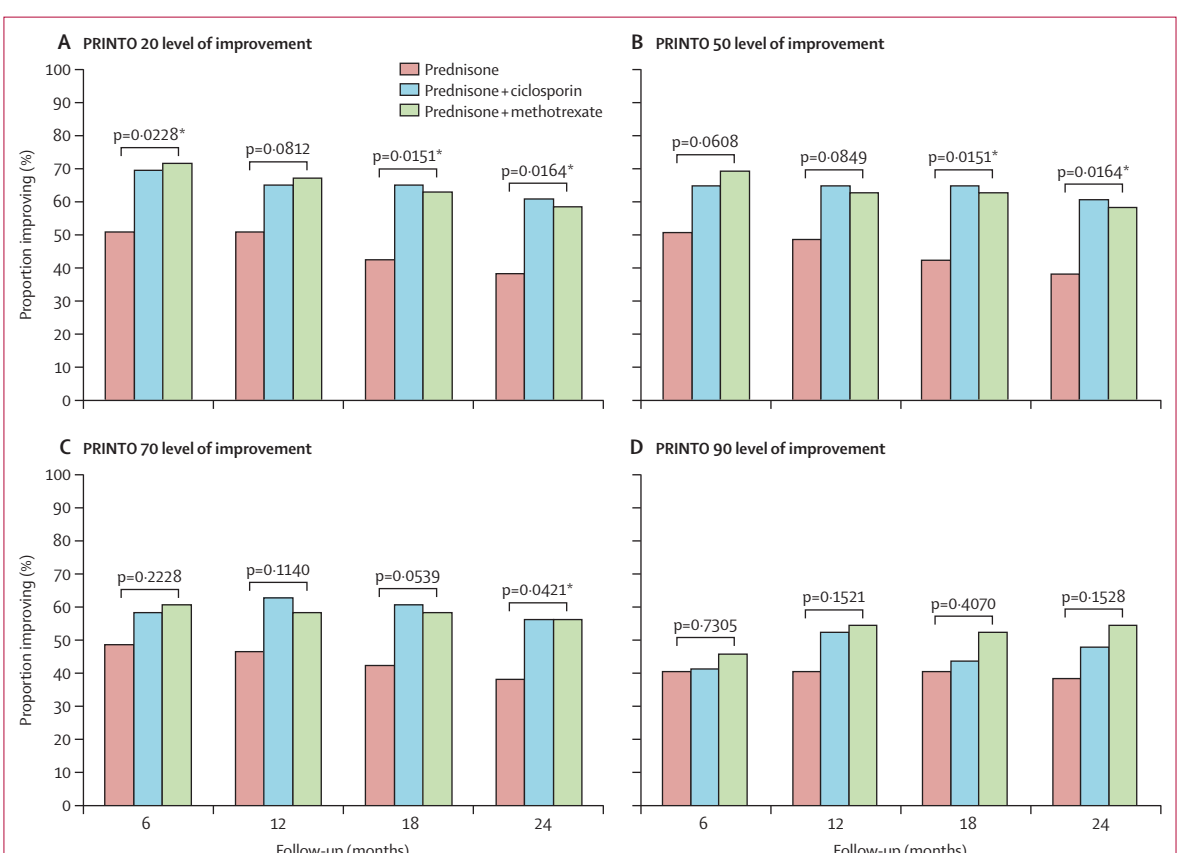

Figure 2: **Juvenile dermatomyositis PRINTO levels of improvement at 6, 12, 18, and 24 months (short-term primary and secondary outcomes)**
*Difference between prednisone alone and the two combination groups is significant.

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 17 patients randomised to prednisone plus methotrexate (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

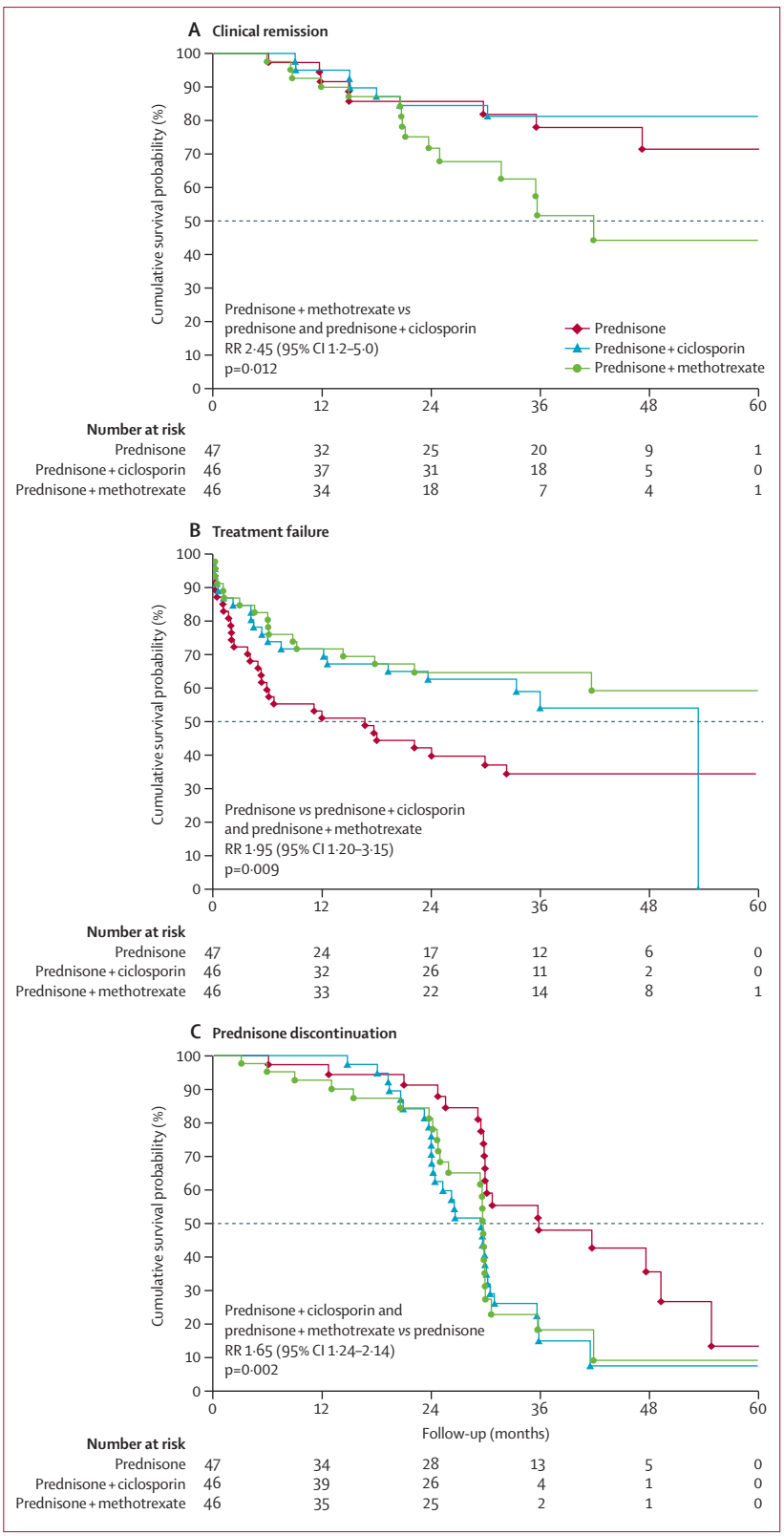

Figure 3: **Kaplan-Meier survival curves for clinical remission, treatment failure, and prednisone discontinuation (long-term primary and secondary outcomes)**

pp 5–7), with changes occurring mainly in the initial 6 months (appendix pp 8–10).

To assess the robustness of long-term efficacy outcomes, we did a sensitivity analysis in which nine children who withdrew consent and eight children who were lost to follow up before month 6 were excluded (figure 1). Results were unchanged, with p values remaining significant (data not shown).

Table 2 summarises adverse events that arose in at least 5% of children in one of the three study groups. The complete list of adverse events is reported in the appendix (pp 11–15). A significant increase in the frequency of adverse events in skin and subcutaneous tissues and gastrointestinal and general disorders was noted in children assigned prednisone plus ciclosporin. Infections and infestations were significantly increased in patients allocated prednisone plus ciclosporin and prednisone plus methotrexate. Hypertrichosis, hirsutism, and abdominal pain were significantly increased in children assigned prednisone plus ciclosporin.

	Prednisone (n=47)	Prednisone plus ciclosporin (n=46)	Prednisone plus methotrexate (n=46)	p
Adverse events	51	128	74	..
Median (range) adverse events per patient	0 (0–8)	1·5 (0–20)	1 (0–8)	0·004
Patients with serious adverse event	1 (2%)	5 (11%)	2 (4%)	0·17
Patients with adverse event leading to permanent or temporary withdrawal	1 (2%)	10 (22%)	10 (22%)	0·009
Skin and subcutaneous tissue disorders	10 (21%)	27 (59%)	9 (20%)	<0·0001
Hypertrichosis	5 (11%)	8 (17%)	1 (2%)	0·04
Hirsutism	1 (2%)	11 (24%)	1 (2%)	0·0002
Alopecia	1 (2%)	4 (9%)	2 (4%)	..
Gastrointestinal disorders	9 (19%)	24 (52%)	9 (20%)	0·0004
Nausea	3 (6%)	4 (9%)	4 (9%)	..
Abdominal pain or abdominal pain upper*	2 (4%)	7 (15%)	0	0·008
Infections and infestations	5 (11%)	14 (30%)	14 (30%)	0·03
Endocrine disorders	9 (19%)	6 (13%)	9 (20%)	..
Cushing's syndrome or Cushingoid*	9 (19%)	6 (13%)	9 (20%)	..
Investigations	3 (6%)	8 (17%)	6 (13%)	..
Weight increased	3 (6%)	1 (2%)	3 (7%)	..
Blood creatinine increased	0	3 (7%)	0	..
Nervous system disorders	3 (6%)	9 (20%)	2 (4%)	..
Headache	1 (2%)	5 (11%)	1 (2%)	..
General disorders and administration site conditions	1 (2%)	9 (20%)	2 (4%)	0·008
Musculoskeletal and connective tissue disorders	1 (2%)	5 (11%)	4 (9%)	..
Psychiatric disorders	2 (4%)	5 (11%)	4 (9%)	..
Metabolism and nutrition disorders	3 (6%)	4 (9%)	4 (9%)	..
Vascular disorders	2 (4%)	7 (15%)	1 (2%)	..
Cardiac disorders	0	3 (7%)	1 (2%)	..
Tachycardia	0	3 (7%)	0	..
Eye disorders	0	3 (7%)	3 (7%)	..

Adverse events are reported according to the Medical Dictionary for Regulatory Activities (MedDRA) classification by system organ class. Only events that occurred in at least 5% of patients in one of the three treatment groups are reported. 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 related preferred terms.

Table 2: **Adverse events**

Eight (6%) of 139 patients had a serious adverse event (appendix p 16); all were known events that could arise during treatment with the allocated drugs. One serious adverse event was reported in the prednisone group (subcutaneous abscess attributed to prednisone), five were noted in the prednisone plus ciclosporin group (one posterior reversible encephalopathy syndrome, attributed to ciclosporin [drug stopped]; one convulsion attributed to ciclosporin [drug stopped]; one deep vein thrombosis attributed to prednisone [drug stopped]; one appendicitis; and one sepsis in the context of acute pneumonia), and two were recorded in the prednisone plus methotrexate group (one paronychia not related to any drug [methotrexate stopped for psychological intolerance]; one dermohypodermitis [both drugs stopped]). No deaths happened during the study and no pregnancies were reported.

One adverse event leading to temporary or permanent drug discontinuation was noted in the prednisone group (hypersensitivity), 13 (in ten patients) were recorded in the prednisone plus ciclosporin group (two alopecia, one each of nausea and vomiting, appendicitis, increase in serum creatinine, abdominal pain, vomiting, gastritis erosive, hirsutism, hypertension, sepsis, convulsion, and posterior reversible encephalopathy syndrome), and 11 (in ten patients) were reported in the prednisone plus methotrexate group (two increases in aminotransferase enzymes, one each of nausea, hepatitis, hair loss, hirsutism, lung disorder, injection-site oedema, palpitations, Cushing's syndrome, and dermo-hypodermitis).

No severe (grade 4) laboratory abnormalities were noted with respect to white-blood cells, neutrophils, lymphocytes, haemoglobin, platelets, blood urea nitrogen, and creatinine. Calcinosis was noted in seven (15%) children assigned prednisone, six (13%) patients allocated prednisone plus ciclosporin, and 13 (28%) of those randomised to prednisone plus methotrexate ($p=0 \cdot 12$).

Discussion

Our findings suggest that combination treatment with prednisone plus either ciclosporin or methotrexate is superior to prednisone monotherapy in patients with juvenile dermatomyositis, at 6 months and after at least 24 months of treatment. Both time to clinical remission (clinically inactive disease persisting for at least 6 continuous months) and time to clinically inactive disease favoured the combination of prednisone plus methotrexate over the combination of prednisone plus ciclosporin or prednisone alone. Furthermore, prednisone plus either methotrexate or ciclosporin was superior to prednisone alone when time to 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.[5–9,27] 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.[28] 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.[13–15]

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.

Contributors

The study was designed jointly by NR, AP, AM, and AR. Data were collected by all PRINTO investigators. The statistical analysis was done by AP and NR. The first and subsequent versions of the report were written by NR and AP, edited by AM and AR, and revised critically by all authors. All authors participated in data collection, data analysis, and data interpretation, and have approved the final study report.

Declaration of interests

NR reports grants from Agenzia Italiana del Farmaco (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 personal fees from Abbott, AbbVie, Astellas, Alter, AstraZeneca, Boehringer, Bristol-Myers Squibb, CD-Pharma, Celgene, Crescendo Bio, EMD Serono, Hoffman-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Vertex Pharmaceuticals, and Servier outside the submitted work. AP reports personal fees from Boehringer, Omniprex, and Novartis outside the submitted work. AR reports grants from AIFA during the conduct of the study; grants from Pfizer outside the submitted work; and personal fees from AbbVie, Bristol-Myers Squibb, Novartis, Pfizer, Roche, and Johnson & Johnson outside the submitted work. MTa reports personal fees from Novartis, Sanofi, Genzyme, Biogen, TEVA, and Shire outside the submitted work. RCu reports grants from Istituto Giannina Gaslini during the conduct of the study; and personal fees from Roche, Novartis, Bristol-Myers Squibb, Lily, GlaxoSmithKline, and Pfizer outside the submitted work. NW reports personal fees from Novartis and Pfizer outside the submitted work; and grants from AbbVie and Roche outside the submitted work. PD reports grants from Istituto Giannina Gaslini during the conduct of the study; other financial relationships with Roche outside the submitted

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. MTr 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, BM, TA, FD, VG, CB, RCi, VF, BF, and CP report grants from Istituto Giannina Gaslini during the conduct of the study. MF, GS, KB, FC, MTA, AC-C, GC, RJ, PQ, RR, BB, AMe, EA-L, TH, VV, CW, and SA declare no competing interests.

Acknowledgments

The Italian Agency of Drug Evaluation (AIFA), the Istituto Giannina Gaslini (Genoa, Italy), and the Myositis Association (USA) provided funding for the work of the PRINTO coordinating centre. We thank the children and their families who participated in this study; Simona Angioloni, Luca Villa, Michele Pesce, Irene Gregorini, and Chiara Pallotti from the PRINTO coordinating centre; and staff at the PRINTO participating centres: Graciela Espada, Stella Maris Garay (Argentina); Roberto Marini (Brazil); Marine Desjonqueres, Chantal Job Deslandre, Anne Pagnier, Georges Picherot, Christine Soler (France); Yosef Uziel (Israel); Patrizia Barone, Loredana Lepore, Silvana Martino (Italy); Valda Stanevicha (Latvia); Ruben Burgos-Vargas (Mexico); Rebecca Ten Cate (Netherlands); Jelena Vojinovic (Serbia); Anders Fasth (Sweden); and Elizabeth Candell Chalom (USA).

References

1 Ravelli A, Trail L, Ferrari C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: a multinational, multicenter study of 490 patients. *Arthritis Care Res (Hoboken)* 2010; **62:** 63–72.

2 Feldman BM, Rider LG, Reed AM, Pachman LM. Juvenile dermatomyositis and other idiopathic inflammatory myopathies of childhood. *Lancet* 2008; **371:** 2201–12.

3 Mendez EP, Lipton R, Ramsey-Goldman R, et al. US incidence of juvenile dermatomyositis, 1995–1998: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Registry. *Arthritis Rheum Arthritis Care Res* 2003; **49:** 300–05.

4 Gordon PA, Winer JB, Hoogendijk JE, Choy EH. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. *Cochrane Database Syst Rev* 2012; **8:** CD003643.

5 Hasija R, Pistorio A, Ravelli A, et al. Approaches for the treatment of new onset and flared juvenile dermatomyositis: an international multicenter PRINTO study. *Arthritis Rheum* 2011; **63:** 3142–52.

6 Guseinova D, Consolaro A, Trail L, et al. Comparison of clinical features and drug therapies among European and Latin American patients with juvenile dermatomyositis. *Clin Exp Rheumatol* 2011; **29:** 117–24.

7 Al Mayouf SM, Laxer RM, Schneider R, Silverman ED, Feldman BM. Intravenous immunoglobulin therapy for juvenile dermatomyositis: efficacy and safety. *J Rheumatol* 2000; **27:** 2498–503.

8 Al-Mayouf S, Al-Mazyed A, Bahabri S. Efficacy of early treatment of severe juvenile dermatomyositis with intravenous methylprednisolone and methotrexate. *Clin Rheumatol* 2000; **19:** 138–41.

9 Heckmatt J, Saunders C, Peters AM, et al. Cyclosporin in juvenile dermatomyositis. *Lancet* 1989; **333:** 1063–66.

10 Ruperto N, Martini A, for the Paediatric Rheumatology International Trials Organisation (PRINTO). Networking in pediatrics: the example of the Pediatric Rheumatology International Trials Organisation (PRINTO). *Arch Dis Child* 2011; **96:** 596–601.

11 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; **292:** 344–47.

12 Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975; **292:** 403–07.

13 Ruperto N, Ravelli A, Murray KJ, et al. Preliminary core sets of measures for disease activity and damage assessment in juvenile systemic lupus erythematosus and juvenile dermatomyositis. *Rheumatology (Oxford)* 2003; **42:** 1452–59.

14 Ruperto N, Ravelli A, Pistorio A, et al. The provisional Pediatric Rheumatology International Trial Organization/American College of Rheumatology/European League Against Rheumatism disease activity core set for the evaluation of response to therapy in juvenile dermatomyositis: a prospective validation study. *Arthritis Rheum* 2008; **59:** 4–13.

15 Ruperto N, Pistorio A, Ravelli A, et al. The pediatric rheumatology international trials organization provisional criteria for the evaluation of response to therapy in juvenile dermatomyositis. *Arthritis Care Res* 2010; **62:** 1533–41.

16 Lovell DJ, Lindsley CB, Rennebohm RM, et al. Development of validated disease activity and damage indices for the juvenile idiopathic inflammatory myopathies: II—the Childhood Myositis Assessment Scale (CMAS), a quantitative tool for the evaluation of muscle function. *Arthritis Rheum* 1999; **42:** 2213–19.

17 Rider LG, Feldman BM, Perez MD, et al. Development of validated disease activity and damage indices for the juvenile idiophatic inflammatory myopathies: I—physician, parent, and patients global assessments. *Arthritis Rheum* 1997; **40:** 1976–83.

18 Bode RK, Klein-Gitelman MS, Miller ML, Lechman TS, Pachman LM. Disease activity score for children with juvenile dermatomyositis: reliability and validity evidence. *Arthritis Rheum* 2003; **49:** 7–15.

19 Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum* 1994; **37:** 1761–69.

20 Ruperto N, Ravelli A, Pistorio A, et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries: review of the general methodology. *Clin Exp Rheumatol* 2001; **19:** S1–S9.

21 Landgraf JM, Abetz L, Ware JE. The CHQ user's manual, 1st edn. Boston: The Health Institute, New England Medical Center, 1996.

22 Oddis CV, Rider LG, Reed AM, et al. International consensus guidelines for trials of therapies in the idiopathic inflammatory myopathies. *Arthritis Rheum* 2005; **52:** 2607–15.

23 Ruperto N, Ravelli A, Cuttica R, et al. The Pediatric Rheumatology International Trials Organization criteria for the evaluation of response to therapy in juvenile systemic lupus erythematosus: prospective validation of the disease activity core set. *Arthritis Rheum* 2005; **52:** 2854–64.

24 Rider LG, Prasad K, Feldman BM, et al. Relationships among laboratory tests and global disease activity assessments in juvenile dermatomyositis. *Arthritis Rheum* 1996; **39** (suppl)**:** S191.

25 Rider LG. Assessment of disease activity and its sequelae in children and adults with myositis. *Curr Opin Rheumatol* 1996; **8:** 495–506.

26 Ramanan AV, Feldman BM. The role of muscle enzymes in JDM. *Pediatr Rheumatol Online J* 2005; **3:** 1–4.

27 Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis: four year review of nine cases. *Arch Dis Child* 1995; **72:** 25–28.

28 Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum* 2013; **65:** 314–24.