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Therapeutic Approaches in the Treatment of Juvenile Dermatomyositis in Patients With Recent-Onset Disease and in Those Experiencing Disease Flare

An International Multicenter PRINTO Study

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***Objective*. To evaluate response to therapy over a 24-month period in a large prospective international cohort of patients with juvenile dermatomyositis (DM).**

***Methods*. The study included 145 patients with recent-onset juvenile DM and 130 juvenile DM patients experiencing disease flare, all of whom were <18 years old. Disease activity parameters and therapeutic approaches in 4 geographic areas were analyzed at baseline and at 6, 12, and 24 months. Response was assessed according to the Pediatric Rheumatology International Trials Organization (PRINTO) juvenile DM response criteria, and data were reported "as observed" and in the intent-to-treat (ITT) population.**

***Results*. Patients with recent-onset juvenile DM at baseline had higher baseline disease activity and greater improvement over 24 months when compared to juvenile DM patients experiencing disease flare at baseline. Methotrexate (MTX) or high-dose corticosteroids were administered more frequently to patients with recent-onset juvenile DM, compared to juvenile DM patients experiencing disease flare, who were more likely to receive cyclosporine. Compared to patients from Western and Eastern Europe, a higher proportion of patients from South and Central America and North America received pulse steroids, and the average steroid dosage was higher in the North American and South and Central American patients. The use of MTX was similar in all 4 regions, while cyclosporin A was more frequently used in Western Europe. In the "as observed" analysis, 57.9% of the patients with recent-onset juvenile DM and 36.4% of the patients experiencing disease flare ($P < 0.001$) reached at least a 70% response by PRINTO criteria at 6 months; these proportions had increased at month 24 to 78.4% and 51.2%, respectively ($P < 0.001$). Corresponding results of the ITT analysis**

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were much lower, with only one-third of the patients able to maintain the initial assigned therapy over 24 months.

***Conclusion*. Patients with recent-onset juvenile DM are more likely to achieve significant clinical improvement over 24 months, when compared to patients experiencing flares of juvenile DM. Internationally, various therapeutic approaches are used to treat this disease.**

Juvenile dermatomyositis (DM) is an idiopathic inflammatory myopathy associated with systemic vasculopathy. Its main characteristics are specific vasculitic changes in the skin and inflammation of the muscle, causing progressive muscle weakness. It is the most common of the juvenile idiopathic inflammatory myopathies, with an annual incidence of 2–4 cases per million children (1–3). Although a marked improvement in long-term outcome and survival rate in juvenile DM patients has been recently documented (4–7), disease treatment remains largely empirical, and little information is available on standardized evaluation of response to therapy based on current treatment options.

In 2000, the Pediatric Rheumatology International Trials Organization (PRINTO) (8) started a multinational effort to develop and validate a core set of outcome variables, known as the PRINTO/American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) juvenile DM core set, and related response criteria to evaluate response to therapy in juvenile DM, known as the PRINTO juvenile DM response criteria (9–11). As part of this international effort, we have also collected standardized information on therapeutic approaches currently being used for the care of patients with juvenile DM.

The aim of this post hoc analysis was to evaluate response to therapy over a 24-month period according to the PRINTO juvenile DM response criteria in a large international prospective cohort of patients who have been recently diagnosed as having, or are experiencing disease flares of, juvenile DM. A secondary aim was to evaluate current approaches to the treatment of juvenile DM in 4 geographic areas.

PATIENTS AND METHODS

Study design. Enrollment was started in June 2001, and ended in March 2004. The participating PRINTO/Pediatric Rheumatology Collaborative Study Group members were asked to prospectively collect data on clinical, laboratory, and therapeutic modalities in all patients seen consecutively in their units who had the following features: 1) probable or definite juvenile DM as defined by disease criteria (12,13), 2) age younger than 18 years, and 3) disease in an active phase, defined as either the need to start corticosteroid therapy and/or a new immunosuppressive medication or to receive a major increase in the dosage of ongoing corticosteroid and/or other immunosuppressive medications. Patients were excluded from the study if, at baseline, their DM was in drug-induced or spontaneous clinical remission, they were receiving stable therapy, or they had a concomitant serious illness. Data were collected at baseline and at 6, 12, and 24 months. For the purposes of this analysis, we included patients who had at least baseline and 6-month data available. In order to take into account the possible differences in the therapeutic approaches and clinical outcome, patients were grouped into 2 different categories, based on whether they had been recently diagnosed and were previously untreated, or if they had longer disease duration and were experiencing a flare and/or requiring an escalation of therapy. Patients were also divided according to 4 geographic areas: Western Europe and Eastern Europe, and South and Central America and North America. In each center, written or verbal informed consent was obtained from a parent or legal guardian, according to the requirements of the local ethics committees.

PRINTO/ACR/EULAR juvenile DM core set measures. The following 6 PRINTO juvenile DM core set measures (10) were assessed at each time point: 1) physician's global assessment of the patient's overall disease activity, using a 10-cm visual analog scale (VAS) (14); 2) muscle strength, using the Childhood Myositis Assessment Scale (CMAS) (15–17); 3) global disease activity assessment, using the Disease Activity Score (DAS) for juvenile DM (18); 4) functional ability, using the Childhood Health Assessment Questionnaire (C-HAQ) (19–22); 5) parent's global assessment of the patient's overall well-being, using a 10-cm VAS (14,19,20); and 6) health-related quality of life, using the physical summary score of the Child Health Questionnaire (CHQ), parent version (20,23). Scoring and content of all the instruments have been described previously (10).

Treatment history. At each time point, we collected information on the dosage of corticosteroids, methotrexate (MTX), cyclosporin A (CSA), azathioprine (AZA), intravenous immunoglobulin (IVIG), and any other medications used. In addition, as per the inclusion criteria of the main study, data were collected to document any therapy the patient received before the first visit and to note all medications that had recently been introduced or had an important change in dosage.

Evaluation of response to therapy. According to the provisional PRINTO definition of improvement in juvenile DM (11), patients were considered to be improved if they demonstrated $\geq$20% improvement from baseline in any 3 of the 6 core set measures (10), with no more than 1 of the remaining measures, which could not be muscle strength worsening by $>$30% (PRINTO juvenile DM 20). We also evaluated patients by more stringent definitions of improvement, requiring 50%, 70%, and 90% improvement (PRINTO juvenile DM 50, 70, and 90, respectively). For the purposes of this analysis, disease was provisionally defined as clinically inactive if muscle strength was normal (CMAS $\geq$48), physician global assessment of disease activity was $\leq$0.5 cm on a 10-cm VAS, and levels of creatine kinase were normal ($\leq$150 units/liter) while the patient was receiving medication.

Responder data were reported "as observed" and in the intent-to-treat (ITT) population. In the "as observed" analysis, responder status was reported with regard to whatever specific treatment the patient was receiving at the time of the assessment. In the ITT analysis, baseline medications (e.g., steroids alone, steroids plus MTX, steroids plus CSA, etc.) were considered the assigned treatment; if at the followup visit the patient had received a change in therapy (e.g., addition of drugs different from those used at baseline), then the patient was considered a nonresponder to the baseline-assigned treatment for the remaining followup, irrespective of the observed responder status. The hypothesis guiding the ITT analysis was that initial therapeutic choices, based upon the decision of the physician or family, cannot be followed linearly for the entire course of a chronic condition like juvenile DM, and therefore therapeutic modifications, in either dosing, add-on therapy, or drug switching, are necessary to properly control the disease. For the purposes of this report, disease flare has been defined according to the physician's decision to increase, modify, or add corticosteroid therapy and/or a new immunosuppressive agent, as per the inclusion criteria.

Statistical analysis. Data were reported as medians (interquartile range [IQR]) or as absolute numbers and percentages. Quantitative data were analyzed by Kruskal-Wallis nonparametric test, followed by Dunn's test. All comparisons at followup were made using nonparametric analysis of variance (Friedman's test for repeated measurements); post hoc comparisons were made by Wilcoxon's matched pairs test with P values corrected by Bonferroni adjustment (P_{corr}). Categorical data were compared among groups of patients (4 geographic areas) by chi-square test or Fisher's exact test with Bonferroni correction for multiple comparisons. Data were entered in an Access XP database and analyzed with Excel XP (Microsoft), XLSTAT 6.1.9 (Addinsoft), Statistica 6.0 (StatSoft), and Stata 7.0 (Stata Corporation) by 2 of the authors (AP and NR).

RESULTS

Demographic characteristics. A total of 294 patients were enrolled from 97 centers in 36 countries as follows: Argentina (n = 35), Australia (n = 2), Austria (n = 2), Belgium (n = 3), Brazil (n = 28), Bulgaria (n = 3), Canada (n = 3), Chile (n = 3), Costa Rica (n = 7), Croatia (n = 5), Cuba (n = 1), Czech Republic (n = 5), Denmark (n = 3), Finland (n = 2), France (n = 11), Germany (n = 20), Greece (n = 6), Hungary (n = 1), Israel (n = 4), Italy (n = 33), Latvia (n = 3), Mexico (n = 3), Netherlands (n = 17), Norway (n = 5), Poland (n = 4), Portugal (n = 6), Serbia and Montenegro (n = 6), Singapore (n = 1), Slovakia (n = 3), Slovenia (n = 1), Spain (n = 10), Sweden (n = 2), Switzerland (n = 11), Turkey (n = 6), the UK (n = 24), and the US (n = 15). The investigators at each center are listed in Appendix A. Of the 294 patients enrolled, 19 were excluded from the study (9 patients were excluded for polymyositis without cutaneous manifestations, 1 patient was later diagnosed as having muscular dystrophy, and 9 patients were lost to followup soon after the baseline visit).

Of the remaining 275 patients included in the analysis (94%) who had data available for at least baseline and 6-month assessments, 168 patients were female (61%) and 107 were male (39%); the median age at disease onset was 7.2 years (IQR 4.3–10.2 years), and median disease duration at baseline was 7.7 months (IQR 2.7–25.3 months) in the entire group, 3.0 months (IQR 1.6–5.6 months) in patients with recent-onset juvenile DM (n = 145), and 27.3 months (IQR 12.7–49.2 months) in those experiencing disease flare later in the course of juvenile DM (n = 130). Seventy-seven patients (28%) were lost to followup at 12 months and 10 additional patients (4%) were lost to followup at 24 months. A total of 174 patients (63%) had all 4 assessments available; there were no differences in sex distribution, age at onset, disease duration, age at first visit, or other baseline characteristics between the 174 patients with all 4 assessments available and the remaining 101 patients lost to followup after month 6 (data not shown).

Table 1 shows the median changes over time, from baseline to month 24, in the PRINTO juvenile DM core set variables in the 2 groups of patients (those with a recent diagnosis versus those experiencing disease flare). At baseline, patients experiencing disease flare had statistically significantly less severe muscle involvement, less disease activity, less disability, and better scores on the parental global assessment of the patient's overall well-being, when compared to patients with recent-onset juvenile DM. There were no statistically significant differences between the 2 groups in terms of the physician's global evaluation of the patient's overall disease activity and health-related quality of life as assessed with the CHQ.

In both groups of patients, all measures showed a statistically significant change over time ($P < 0.0001$). In comparison to baseline values, improvement was most pronounced during the initial 6 months and continued up to month 12; additionally, improvement was more pronounced in the patients with recent-onset juvenile DM than in the patients experiencing disease flare. In the subsequent 12 months of followup, measures remained substantially unchanged, with a trend toward a statistically significantly lower level of improvement for patients experiencing disease flare. In particular, the physician's global assessment of disease activity changed from a median baseline value of 5.7 to 0.0 by month 24 in patients with recent-onset disease, as compared to a change from 5.2 to 0.5 in the patients experiencing disease flare. Muscle strength, as measured by the

Table 1. Descriptive characteristics of the PRINTO/ACR/EULAR core set variables for the 275 patients included in the analysis*

Variable	Month 0 (n = 275)	Month 6 (n = 275)	Month 12 (n = 198)	Month 24 (n = 188)	P†
Physician's global assessment of the patient's overall disease activity (0–10 cm VAS)					
Patients with recent-onset disease	5.7 (3.9–7.2)	0.7 (0.2–1.9)‡	0.2 (0–0.9)‡	0 (0–1)	<0.0001
Patients experiencing disease flare	5.2 (3.1–6.9)	1.2 (0.4–3.2)‡	0.8 (0–2.2)	0.5 (0–2)§	<0.0001
CMAS (0–52 score)					
Patients with recent-onset disease	22 (12–33)	47 (40–50)‡	49 (44–52)‡	51 (45–52)¶	<0.0001
Patients experiencing disease flare	30 (15–40)§	45 (35–49)‡	47 (40–51)	49 (40–52)	<0.0001
DAS (0–20 score)					
Patients with recent-onset disease	13 (11–15)	4 (3–6)‡	3 (0–6)#	2 (0–5)	<0.0001
Patients experiencing disease flare	12 (9–14)‡	6 (3–9)‡	5 (3–8)§	4 (1–8)§	<0.0001
C-HAQ (0–3 score)					
Patients with recent-onset disease	2 (1.38–2.63)	0.25 (0–0.83)‡	0 (0–0.25)‡	0 (0–0.13)	<0.0001
Patients experiencing disease flare	1.38 (0.75–2.38)§	0.5 (0–1.14)‡	0.13 (0–0.88)§	0.25 (0–1.38)§	<0.0001
Parent's global assessment of the overall patient's well-being (0–10-cm VAS)					
Patients with recent-onset disease	6.3 (3.9–7.8)	0.8 (0–1.9)‡	0.5 (0–1.8)	0.2 (0–0.9)¶	<0.0001
Patients experiencing disease flare	4.9 (2–6.7)§	1.0 (0.2–3.2)‡	0.4 (0–3)	0.2 (0–2.9)	<0.0001
Physical summary score on Child Health Questionnaire (40–60 score)					
Patients with recent-onset disease	29.3 (23.3–38.6)	52.2 (42.5–54.7)‡	53.5 (48.2–55.3)¶	53.1 (49.3–54.9)	<0.0001
Patients experiencing disease flare	34.1 (23.9–45.0)	47.7 (39.7–53.5)‡	52.2 (42.9–54)	50.8 (41.2–53.2)§	<0.0001

* Values are the median (interquartile range). A higher score for the physician's global assessment of patient's overall disease activity, the Disease Activity Score (DAS), the Childhood Health Assessment Questionnaire (C-HAQ), and the parent's global assessment of patient well-being denotes worse disease activity; a lower score for the Childhood Myositis Assessment Scale (CMAS) and physical summary score on Child Health Questionnaire denotes worse disease activity. PRINTO/ACR/EULAR = Pediatric Rheumatology International Trials Organization/American College of Rheumatology/European League Against Rheumatism; VAS = visual analog scale.
† Significance of the change from baseline to month 24, by repeated-measures nonparametric analysis of variance.
‡ Corrected P (P_{corr}) < 0.001 versus previous assessment.
§ $P < 0.05$ versus patients with recent-onset disease.
¶ $P_{corr} < 0.05$ versus previous assessment.
# $P_{corr} < 0.01$ versus previous assessment.

CMAS, reached values close to normal (median score 46) by month 6 in both groups and remained constant thereafter. Similarly, the DAS showed a statistically significant change in the initial 6 months that was maintained in the following 18 months in both groups.

These observations were substantially confirmed by the change in the parent's reported outcomes, such as the parent's global assessment of overall well-being and pain and the C-HAQ, but some degree of physical disability remained at month 24 in those patients who had been experiencing disease flare at baseline (median C-HAQ 0.25 versus 0.0 in patients experiencing disease flare versus patients with recent-onset disease). Notably, the physical summary score of the CHQ at baseline was 2 SD below that of the healthy controls in the patients with recent-onset juvenile DM and 1 SD below that of healthy controls in the patients experiencing disease flare, and both groups reached normal levels of physical well-being by month 6, which was maintained thereafter.

Therapeutic approaches over time. Table 2 shows the therapeutic approaches over time in both groups of patients. With regard to treatment at baseline, almost all patients (269 of 275; 98%) were receiving corticosteroids, with 192 (70%) having recently begun taking intravenous pulse or oral steroids, and 91 (33%) being treated with steroids in combination with MTX. The frequency of patients newly starting any corticosteroids or MTX was higher in the group of patients with recent-onset juvenile DM compared to the group experiencing disease flare (corticosteroid use in 90.3% versus 46.9%; MTX in 89.3% versus 52.6%). The same trend was observed in patients treated with pulse corticosteroids. Conversely, CSA was used less frequently in patients with recent-onset juvenile DM compared to patients experiencing disease flare (5.5% versus 27.7%). When IVIG treatment was assessed, there was no statistically significant difference between the 2 groups.

The median dosage of prednisone equivalent at baseline was 1.31 mg/kg/day (IQR 0.78–1.94) in the group of patients with recent-onset disease and 0.75 mg/kg/day (IQR 0.38–1.25) in the group experiencing disease flare; prednisone dosages were decreased over

Table 2. Treatment modalities used at various time points during the study period*

	Month 0 (n = 275)	Month 6 (n = 275)	Month 12 (n = 198)	Month 24 (n = 188)	P†
Patients receiving any steroids					
Patients with recent-onset disease	142/145 (97.9)	139/145 (95.9)	70/103 (68.0)‡	41/98 (41.8)‡	<0.0001
Patients experiencing disease flare	127/130 (97.7)	117/130 (90.0)§	75/95 (78.9)	56/90 (62.2)§¶	<0.0001
Patients starting steroids					
Patients with recent-onset disease	131/145 (90.3)	2/145 (1.4)‡	0/103 (0.0)	2/98 (2.0)	<0.0001
Patients experiencing disease flare	61/130 (46.9)¶	2/130 (1.5)‡	3/95 (3.2)	3/90 (3.3)	<0.0001
Patients receiving pulse steroids					
Patients with recent-onset disease	64/145 (44.1)	21/145 (14.5)‡	8/103 (7.8)	2/98 (2.0)	<0.0001
Patients experiencing disease flare	36/130 (27.7)¶	14/130 (10.8)#	7/95 (7.4)	6/90 (6.7)	<0.0001
Dosage of prednisone equivalent, median (interquartile range) mg/kg/day					
Patients with recent-onset disease	1.31 (0.78–1.94) (n = 138)	0.34 (0.19–0.62)‡ (n = 139)	0.23 (0.13–0.41) (n = 68)‡	0.27 (0.13–0.40) (n = 41)	<0.0001
Patients experiencing disease flare	0.75 (0.38–1.25) (n = 123)¶	0.29 (0.15–0.55) (n = 116)‡¶	0.18 (0.10–0.35) (n = 73)#	0.16 (0.08–0.32) (n = 54)§	<0.0001
Patients receiving MTX					
Patients with recent-onset disease	56/145 (38.6)	85/145 (58.6)#	66/103 (64.1)	58/98 (59.2)	0.0001
Patients experiencing disease flare	78/130 (60)¶	79/130 (60.8)	55/95 (57.9)	56/90 (62.2)	0.94
Patients starting MTX					
Patients with recent-onset disease	50/56 (89.3)	32/85 (37.6)‡	12/66 (18.2)§	7/58 (12.1)	<0.0001
Patients experiencing disease flare	41/78 (52.6)¶	8/79 (10.1)‡¶	8/55 (14.5)	10/56 (17.9)	<0.0001
Patients receiving cyclosporin A					
Patients with recent-onset disease	8/145 (5.5)	19/145 (13.1)	12/103 (11.7)	15/98 (15.3)	0.07
Patients experiencing disease flare	36/130 (27.7)¶	34/130 (26.2)¶	19/95 (20.0)	18/90 (20.0)	0.40
Patients receiving IVIG					
Patients with recent-onset disease	21/145 (14.5)	16/145 (11.0)	4/103 (3.9)§	3/98 (3.1)	0.003
Patients experiencing disease flare	17/130 (13.1)	13/130 (10.0)	6/95 (6.3)	6/90 (6.7)	0.27
Patients not receiving any treatment					
Patients with recent-onset disease	–	3/145 (2.1)	10/103 (9.7)§	26/98 (26.5)#	<0.0001
Patients experiencing disease flare	–	2/130 (1.5)	11/95 (11.6)#	13/90 (14.4)¶	0.001

* Except where indicated otherwise, values are the number of patients receiving treatment/number of patients in group (%). MTX = methotrexate; IVIG = intravenous immunoglobulin.
† Significance of the change from baseline to month 24, by repeated-measures nonparametric analysis of variance.
‡ Corrected P (P_{corr}) < 0.001 versus previous assessment.
§ $P_{corr} < 0.05$ versus previous assessment.
¶ $P < 0.05$ versus patients with recent-onset disease.
# $P_{corr} < 0.01$ versus previous assessment.

the course of the study in both groups (especially in the initial 6 months), and remained unchanged thereafter. Pulse steroids were used more frequently at baseline and at 6 months (particularly in the group of patients with recent-onset disease), and to a lesser extent in the following months. At 6 months, >90% of the patients were receving corticosteroids; this had decreased to 73% of all patients at 12 months. At 24 months, patients with recent-onset juvenile DM were less likely to be receiving corticosteroids, compared to patients experiencing disease flare at study baseline (41.8% versus 62.2%). The median dosage of MTX at baseline was 14 mg/m^2/week, and changed little over time in both groups. Five of the 275 patients assessed at 6 months (1.8%), 21 of 198 patients assessed at 12 months (10.6%), and 39 of 188 patients assessed at 24 months (21.3%) were not being treated with any medication, with patients who had recent-onset juvenile DM having discontinued therapy by 24 months at a higher rate than those experiencing disease flare (26.5% versus 14.4%; $P_{corr} < 0.05$).

The observed therapeutic approaches at baseline for the 4 main geographic areas (Western and Eastern Europe and South and Central and North America) are reported in Table 3. Most patients were from Western Europe (56%) and South and Central America (25%), which are the classic catchment areas for PRINTO.

At baseline, in each geographic area, patients with recent-onset juvenile DM were significantly more likely to begin treatment with corticosteroids than patients experiencing disease flare, with the exception of patients from North America, for whom the sample was too small to calculate significance. Similarly, patients with recent-onset disease were more likely to receive pulse steroids when compared with patients experienc-

Table 3. Treatment approaches at baseline in the 4 main geographic areas*

	Western Europe (n = 154; 56%)	Eastern Europe (n = 32; 12%)	South and Central America (n = 68; 25%)	North America (n = 21; 8%)	P†
Patients receiving any steroids					
Patients with recent-onset disease	79/81 (97.5)	16/16 (100)	34/34 (100)	13/14 (92.9)	0.41‡
Patients experiencing disease flare	71/73 (97.3)	16/16 (100)	33/34 (97.1)	7/7 (100)	0.69‡
Patients starting steroids					
Patients with recent-onset disease	70/81 (86.4)	14/16 (87.5)	34/34 (100)	13/14 (92.9)	0.08‡
Patients experiencing disease flare	31/73 (42.5)§	6/16 (37.5)§	19/34 (55.9)§	5/7 (71.4)	0.29‡
Patients receiving pulse steroids					
Patients with recent-onset disease	31/81 (38.3)	3/16 (18.8)	20/34 (58.8)¶	10/14 (71.4)	0.006#
Patients experiencing disease flare	20/73 (27.4)	3/16 (18.8)	11/34 (32.4)§	2/7 (28.6)	0.84‡
Dosage of prednisone equivalent, median (interquartile range) mg/kg/day					
Patients with recent-onset disease	1.27 (0.93–1.94)	1.11 (0.59–1.89)	1.69 (1.21–2.02)	1.08 (0.59–1.51)¶	0.041**
Patients experiencing disease flare	0.52 (0.33–0.94)§	0.82 (0.53–1.20)	1.12 (0.56–1.95)§	1.25 (1.04–1.57)	0.0009**
Patients receiving MTX					
Patients with recent-onset disease	32/81 (39.5)	6/16 (37.5)	10/34 (29.4)	8/14 (57.1)	0.35#
Patients experiencing disease flare	42/73 (57.5)§	12/16 (75.0)§	18/34 (52.9)§	6/7 (85.7)	0.25‡
Patients starting MTX					
Patients with recent-onset disease	29/32 (90.6)	6/6 (100)	8/10 (80.0)	7/8 (87.5)	0.71‡
Patients experiencing disease flare	18/42 (42.9)§	8/12 (66.7)	12/18 (66.7)	3/6 (50.0)	0.26‡
Patients receiving cyclosporin A					
Patients with recent-onset disease	6/81 (7.4)	2/16 (12.5)	0/34 (0)	0/14 (0)	0.18‡
Patients experiencing disease flare	29/73 (39.7)§	3/16 (18.8)	4/34 (11.8)§	0/7 (0)	0.004‡
Patients receiving IVIG					
Patients with recent-onset disease	8/81 (9.9)	3/16 (18.8)	7/34 (20.6)	3/14 (21.4)	0.27‡
Patients experiencing disease flare	12/73 (16.4)	4/16 (25.0)	1/34 (2.9)	0/7 (0)	0.07‡

* Except where indicated otherwise, values are the number of patients receiving treatment/number of patients in group (%). All P values were adjusted by Bonferroni method (P_{corr}). MTX methotrexate; IVIG = intravenous immunoglobulin.
† Significance of the difference among all 4 groups.
‡ By Fisher's exact test.
§ Significant difference in comparison to patients with recent-onset disease.
¶ $P_{corr} < 0.05$ versus patients experiencing disease flares.
# By chi-square test.
** By Kruskal-Wallis test.

ing disease flare, especially if they were in North America (71.4% versus 28.6% in patients experiencing disease flare) and South and Central America (58.8% versus 32.4%; $P_{corr} < 0.05$). Overall, the median prednisone equivalent dosage was significantly higher in patients with recent-onset juvenile DM (median between 1.08 mg/kg/day and 1.69 mg/kg/day in the 4 geographic groups) as compared to daily prednisone dosage in patients experiencing disease flare (median between 0.52 mg/kg/day and 1.25 mg/kg/day in the 4 geographic groups). South American patients with recent-onset juvenile DM tended to receive a higher baseline dosage of corticosteroids, with a median of 1.69 mg/kg/day, as compared to a range of 1.08–1.27 mg/kg/day in the other geographic areas. The starting prednisone equivalent dosages for patients experiencing disease flare were higher for South and Central America and North America (median 1.12 mg/kg/day and 1.25 mg/kg/day, respectively) in comparison to both Western and Eastern European locations (median 0.52 mg/kg/day and 0.82 mg/kg/day, respectively).

The use of MTX at baseline was similar in all 4 regions for both groups of patients, with no statistically significant differences (although North American patients were treated with it the most); patients experiencing disease flare were more likely to receive MTX as compared to patients with recent-onset disease. CSA was more frequently used in Western Europe, especially in patients experiencing disease flare, and it was not used at all in North America. The proportion of patients with recent-onset juvenile DM receiving IVIG was highest in North and South and Central America, while the proportion of patients experiencing disease flare who received IVIG was highest in Western and Eastern Europe.

Response to therapy according to the PRINTO juvenile DM response criteria. The PRINTO 20, 50, 70, and 90 juvenile DM response criteria for improvement

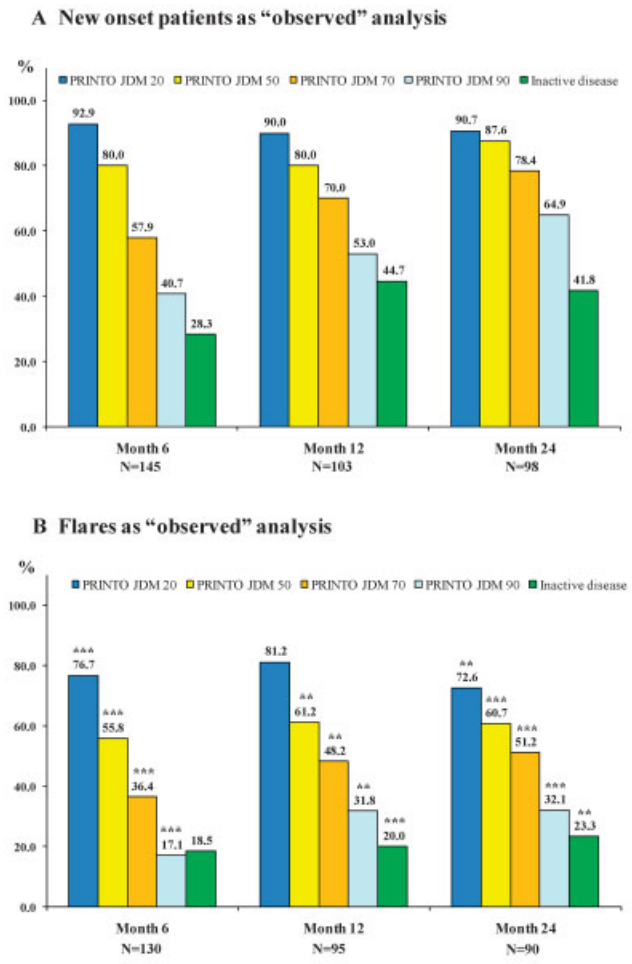

Figure 1. Pediatric Rheumatology International Trials Organization juvenile dermatomyositis (JDM) 20%, 50%, 70%, and 90% improvement (PRINTO juvenile DM 20, 50, 70, and 90, respectively) and clinically inactive disease status over time in the "as observed" analysis. **A**, Responder status in the group of patients with recent-onset juvenile DM. **B**, Corresponding results in the group of patients who experienced disease flare later in the course of juvenile DM. *P* values are versus the group with recent-onset juvenile DM, at the corresponding time point.

and the number of patients considered to have inactive disease while receiving medication in the "as observed" analysis are reported in Figures 1A and B. At the 6-month assessment, the PRINTO 20, 50, 70, and 90 levels of response were significantly higher in patients with recent-onset juvenile DM when compared with the group of patients experiencing disease flare (e.g., PRINTO 50 response criteria were met in 80% of patients versus 55.8%, respectively; $P < 0.001$). Similar significant differences were observed at months 12 and 24; patients with recent-onset juvenile DM were more likely to respond or to reach a status of inactive disease. The greatest level of improvement was reached in the initial 6 months, and was maintained or improved upon thereafter. When more stringent response criteria of improvement were considered, we found that a PRINTO juvenile DM 70 level of response was reached at 6 months by 57.9% of patients with recent-onset juvenile DM compared to 36.4% of the patients experiencing juvenile DM flares ($P < 0.001$), with steady increases over time to 78.4% and 51.2% ($P < 0.001$),

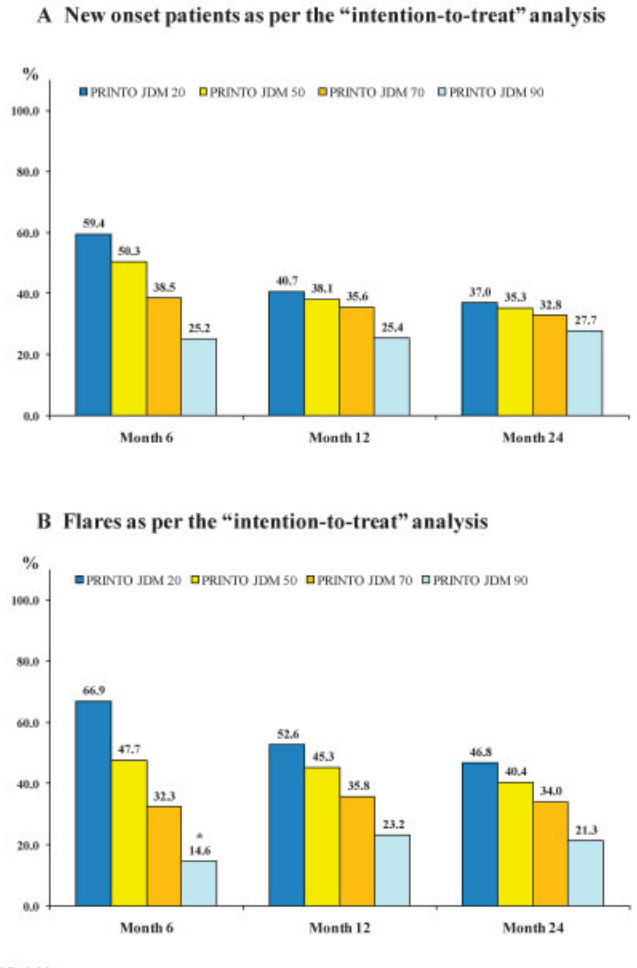

Figure 2. PRINTO juvenile DM 20, 50, 70, and 90 and clinically inactive disease status over time in the intent-to-treat analysis. **A**, Responder status in the group of patients with recent-onset juvenile DM. **B**, Corresponding results in the group of patients who experienced disease flare later in the course of the disease. *P* value is versus the group with recent-onset juvenile DM, at the corresponding time point. See Figure 1 for definitions.

respectively, by 24 months. The same trend was observed in analyses of the most stringent level of improvement, with an inactive disease status reached at 24 months by 41.8% of patients with recent-onset disease and by 23.3% of those experiencing disease flare.

The corresponding levels of improvement were lower in the ITT population when compared to the "as observed" analysis (Figures 2A and B). Additionally, in the ITT population, there were no significant differences at any time point between the patients with recent-onset juvenile DM and those experiencing disease flare. By 24 months, a PRINTO 90 level of response had been reached by 32.8% of patients with recent-onset disease and 34% of those experiencing disease flare, with a nonsignificant trend toward more responders in the subgroup of patients with disease flare. Further investigation revealed that results were comparable when all analyses were repeated in the 174 of 275 patients (63%) who had all 4 assessments available (data not shown).

DISCUSSION

In this large international prospective cohort of patients with juvenile DM, treatment, as agreed upon by the physician and family, resulted in substantial response in the initial 6 months. The response increased or was maintained over time and was significantly higher in patients with recent-onset juvenile DM as compared to patients with juvenile DM who experienced disease flare during the course of disease.

A multinational effort was set up by PRINTO and other organizations in order to develop and validate a core set of outcome variables and a definition of clinical improvement for evaluating response to therapy in inflammatory myopathies of adults and children (9–11,24–27). One of the objectives was to investigate treatment results using standardized and comparable measures. As assessed by the PRINTO juvenile DM core set, the children in this cohort showed the greatest improvement in the initial 6 months of treatment. The improvement in the individual PRINTO juvenile DM core set parameters was maintained through the following 18 months, resulting in levels that were close to normal for most of the variables assessed. These results were essentially similar in the 2 groups of juvenile DM patients examined (those with recent-onset disease and those experiencing disease flare), although there was a trend toward greater improvement over time in the first group. The higher level of disease activity observed in the patients with recent-onset juvenile DM at baseline may partially explain the greater improvement observed over time, when compared with the patients who were experiencing disease flare at baseline. Similar to findings in the current study, Seshadri et al (28) reported that there was little difference in efficacy outcome in patients treated at baseline with aggressive therapy (pulse steroids or oral steroids 5–30 mg/kg/day) when compared to patients receiving standard therapy (steroids 1–2 mg/kg/day).

Treatment of juvenile DM, like treatment of DM, is largely empirical, since, to date, no randomized trials have been conducted. After the introduction of corticosteroid therapy in the 1970s, mortality was greatly reduced (3), with a concurrent marked improvement in functional outcomes (4). In order to limit or prevent the well-known corticosteroid toxicity in children who are still growing, and to prevent the occurrence of subsequent disease flares, it has become standard practice to administer corticosteroids either orally or as pulse therapy (29), as well as to combine corticosteroids with other treatment such as MTX (30–33), CSA (34–36), IVIG (37–41), and other medications, as corticosteroid-sparing agents.

The study presented herein demonstrates that corticosteroids remain the most important treatment in controlling disease at onset. Corticosteroids were administered orally, with a relatively high median dosage (1.31 mg/kg/day), in almost all patients with recent-onset disease, with >40% of patients receiving additional pulse corticosteroids. In contrast, patients who had had longer disease duration and were treated for a disease flare tended to receive lower baseline corticosteroid dosages, and were more likely to receive steroid-sparing therapies, such as MTX or CSA. Corticosteroid dosages were steadily decreased during the initial 6 months and were maintained after that time point at lower dosages in both of the groups examined, but patients with recent-onset juvenile DM were more likely to completely discontinue treatment with corticosteroids. Combination therapy with other immunosuppressive medication at baseline (particularly MTX) was commonly used in all 4 geographic regions and increased steadily in the subsequent months of treatment as a steroid-sparing agent or to prevent flares, with ~60% of children having received a course of MTX over a 2-year span. Other medications, such CSA, were more frequently used in patients experiencing juvenile DM flare who had longer disease duration, while IVIG was used less frequently in these patients, perhaps reflecting the low availability and high cost of this treatment modality.

When baseline was analyzed in the 4 main geographic PRINTO catchment areas, there were differ-

ences in the initial therapeutic approach for patients with recent-onset juvenile DM, with pulse corticosteroids being prescribed most frequently in North and South and Central America, followed by Western Europe; CSA appeared to be more frequently prescribed in Western and Eastern Europe for both patients with recent-onset disease and those experiencing disease flare. South and Central American physicians tended to prescribe higher initial dosages of corticosteroids, especially in patients with recent-onset disease. MTX was uniformly used in all 4 geographic areas, in higher proportions in patients experiencing disease flare than in patients with recent-onset disease. Our observations are consistent with those of Stringer et al (42), who reported that, among the majority of North American pediatric rheumatologists, corticosteroids and MTX appear to be the standard initial treatment approach for typical cases of juvenile DM, with variability in the route of administration.

The lack of randomized trials and internationally agreed-upon guidelines for treatment of juvenile DM may explain differences that are based on personal practice and experience, local attitudes, and drug availability. Despite these differences in therapeutic approaches, children in our study showed improvement over time regardless of which therapy was used. The main trend in treatment is to use corticosteroids initially, followed by a careful tapering of corticosteroids and then introduce a second-line agent, such as MTX.

To the best of our knowledge, this is the first report on response to therapy as determined by standardized response criteria for evaluating improvement. The analysis of response to therapy according to the PRINTO juvenile DM response criteria was performed in 2 ways. In the "as observed" analysis, patients were classified as responders based on their status on the day of the assessment, and independent of changes in treatment that may have occurred. By this method, the response rate according to the PRINTO juvenile DM 20 response criteria (or the more stringent 50, 70, and 90 response criteria) appeared to be satisfactory over time, with 64.9% of the group of patients who had recent-onset disease exhibiting at least a 90% improvement after 2 years of treatment. In patients who were experiencing disease flare at baseline, the corresponding level of improvement was significantly lower, indicating that in this group of patients, whose disease relapsed over time, disease control was more difficult to achieve. This observation indicates that therapeutic response is less likely to occur when a patient experiences relapse later in the course of the disease as compared to the untreated patients with recent-onset disease.

In the ITT analysis, patients were assessed based on the initial treatment chosen by the local physician, and any subsequent major deviation (e.g. add-on therapy, switch to alternative medication, or major increase in dosage, especially in corticosteroids) resulted in a classification of the patient's disease as nonresponsive.

When planning for the ITT analysis was begun, our hypothesis was that the initial treatment, thought to be the best choice for each patient, cannot be linearly followed in a chronic condition like juvenile DM, and that deviations from the initial treatment are necessary and would result in lower corresponding levels of response than with the "as observed" analysis. Our results in fact confirmed that levels of improvement in the ITT analysis were lower than in the "as observed" analysis both among patients with recent-onset disease and among those experiencing disease flare. In addition, when the 2 groups of patients were assessed in the ITT analysis, there appeared to be no significant difference in the level of response to treatment. The initial assigned treatment could be maintained in only approximately one-third of patients with recent-onset juvenile DM and a slightly greater proportion of the patients experiencing disease flare.

The discrepancy observed in the results of our "as-observed" and ITT analyses emphasizes the well-known differences between daily clinical practice, in which treatment modalities are more liberal and are modified according to physician interpretation of current patient status, and clinical trials, in which the assigned treatment is the cornerstone of the analysis and any deviation must be counted in the responder status. Our results are consistent with those of Pincus et al, who argued that only 30% of the rheumatoid arthritis population seen in clinical practice would be eligible for inclusion in a clinical trial, and therefore that the results of the clinical trials, while of utmost importance, cannot automatically be translated to similar levels of response in the treatment of chronic rheumatic conditions in clinical practice (43,44).

A limitation of our study is that the treatment was assigned based on physician decision, and the study was not designed or conducted as a randomized clinical trial. However, the large number of patients from many countries, and our use of standardized assessment methods to evaluate response to therapy, is the main strength of this prospective study.

In conclusion, in the context of current clinical practices for the treatment of juvenile DM, patients with

recent-onset disease were more likely to exhibit significant clinical improvement (up to 90%), when compared to patients experiencing disease flare, over a 24-month period. In the 4 geographic areas analyzed, several differences in the initial therapeutic approaches were noted.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ruperto had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Hasija, Pistorio, Ravelli, Demirkaya, Wouters, Philippet, Martini, Ruperto.

Acquisition of data. Ravelli, Demirkaya, Guseinova, Malattia, Canhao, Harel, Foell, Wouters, De Cunto, Huemer, Kimura, Mangge, Minetti, Nordal, Philippet, Garozzo, Ruperto.

Analysis and interpretation of data. Hasija, Pistorio, Ravelli, Demirkaya, Klubchandani, Wouters, Martini, Ruperto.

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