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SPECIAL ARTICLE

The Provisional Paediatric Rheumatology International Trials Organisation/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

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This core set has been approved by the American College of Rheumatology (ACR) Board of Directors as Provisional. This signifies that the core set has been quantitatively validated using patient data, but it has not undergone validation based on an external data set. All ACR-approved core sets are expected to undergo intermittent updates.

Objective. **To validate a core set of outcome measures for the evaluation of response to treatment in patients with juvenile dermatomyositis (DM).**

Methods. **In 2001, a preliminary consensus-derived core set for evaluating response to therapy in juvenile DM was established. In the present study, the core set was validated through an evidence-based, large-scale data collection that led to the enrollment of 294 patients from 36 countries. Consecutive patients with active disease were assessed at baseline and after 6 months. The validation procedures included assessment of feasibility, responsiveness, discriminant and construct ability, concordance in the evaluation of response to therapy between physicians and parents, redundancy, internal consistency, and ability to predict a therapeutic response.**

Results. **The following clinical measures were found to be feasible, and to have good construct validity, discriminative ability, and internal consistency; furthermore, they were not redundant, proved responsive to clinically important changes in disease activity, and were associated strongly with treatment outcome and thus were included in the final core set: 1) physician's global assessment of disease activity, 2) muscle strength, 3) global disease activity measure, 4) parent's global assessment of patient's well-being, 5) functional ability, and 6) health-related quality of life.**

Conclusion. **The members of the Paediatric Rheumatology International Trials Organisation, with the endorsement of the American College of Rheumatology and the European League Against Rheumatism, propose a core set of criteria for the evaluation of response to therapy that is scientifically and clinically relevant and statistically validated. The core set will help standardize the conduct and reporting of clinical trials and assist practitioners in deciding whether a child with juvenile DM has responded adequately to therapy.**

INTRODUCTION

Juvenile dermatomyositis (DM) is a multisystem inflammatory disease that affects primarily the skin and muscles. It is the most common of the juvenile idiopathic inflammatory myopathies (IIM), with an annual incidence of 2–4 cases per million children (1,2). Although recent series have documented a marked improvement in long-term

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outcome and survival of juvenile DM patients (3–5), disease treatment remains largely empiric. One of the leading factors that has hampered a rational therapeutic approach to juvenile DM is the lack of standardized and validated measures for assessing the response to therapy (6). This deficiency leads to an inability to accurately evaluate or compare the effectiveness of drug therapies. Recently, the International Myositis Outcome Assessment and Clinical Studies (IMACS) group proposed a core set of outcome measures for inclusion in clinical trials in adult and juvenile IIM and defined the degree of change in each core set measure that is clinically meaningful (7–9); however, until now these proposals have not yet been formally validated in prospective studies or clinical trials.

In recent years, the Paediatric Rheumatology International Trials Organisation (PRINTO) (10), in collaboration with the Pediatric Rheumatology Collaborative Study Group (PRCSG), and with the support of the European Union and the US National Institutes of Health, undertook a multinational effort that aimed to develop and validate a core set of outcome measures and a definition of clinical improvement in patients with juvenile DM, similar to that already done for juvenile idiopathic arthritis (11–13) and for juvenile systemic lupus erythematosus (14,15).

The results of the first part of the study, published previously (16), led to the definition of a preliminary consensus-based core set of domains. Here, we report the results of the second phase of the project, which was aimed at formally validating the preliminary juvenile DM core set for the evaluation of response to therapy through a prospective, large-scale data collection process. Our objective was to further define and validate the preliminary core set to evaluate the response to therapy in patients with juvenile DM.

PATIENTS AND METHODS

Study design. Enrollment began in June 2001 and ended in March 2004. The participating PRINTO/PRCSG members were asked to assess all variables in the preliminary core set, in all patients seen consecutively in their units who had probable or definite diagnosis of juvenile DM (classic DM rash plus at least 2 or 3 of the other Bohan and Peter criteria, respectively [17,18]), were younger than age 18 years, and were experiencing an active phase of their disease, defined as either the need to start corticosteroid therapy and/or a new immunosuppressive medication or, in those receiving ongoing therapy, the need to undergo a major increase in the dosage of corticosteroid and/or immunosuppressive drugs. Six months after the baseline evaluation, the core set variables were reassessed in each patient. We chose this protocol and timeframe to approximate what is usually done in a clinical trial. Patients were excluded from the study if at baseline, they were experiencing drug-induced or spontaneous clinical remission, were receiving stable therapy, or had a concomitant serious illness.

In each center, written or verbal informed consent was obtained from a parent or legal guardian, according to the requirements of the local ethic committees.

Assessment of preliminary core set variables. The following preliminary core set measures were assessed at baseline and 6 months later: 1) the physician's global assessment of the patient's overall disease activity on a 10-cm visual analog scale (VAS) (where 0 = no activity and 10 = maximum activity) (19); 2) muscle strength via the Childhood Myositis Assessment Scale (CMAS) (where 0 = worst and 52 = best) (20–22) and manual muscle testing (MMT) on 8 muscles tested unilaterally (where 0 = worst and 80 = best) (23); 3) serum muscle enzymes (creatine kinase [CK], lactate dehydrogenase, aldolase, aspartate aminotransferase, and alanine aminotransferase) (24–28), whose results were standardized based on the normal values provided by each local laboratory as previously described (14); 4) functional ability via the Childhood Health Assessment Questionnaire (C-HAQ) (where 0 = best and 3 = worst) (29,30); 5) the parent's global assessment of the patient's overall well-being on a 10-cm VAS (where 0 = very well and 10 = very poor) (19,29,30); 6) global assessment of disease activity according to the Disease Activity Score (DAS) (31) and the Myositis Disease

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Activity Assessment (MDAA) (32). Briefly, the DAS is a 20-point scale comprising 2 subscales reflecting skin involvement (ranging from 0 to 9) and muscle inflammation (ranging from 0 to 11), with higher scores indicating greater disease activity. The MDAA combines 2 partially overlapping tools, the Myositis Disease Activity Assessment Visual Analog Scale (MYOACT) and Myositis Intent-to-Treat Activity Index (MITAX), A-E version. The MYOACT is composed of a series of 10-cm VAS that refer to disease activity in the following organs or systems: constitutional, cutaneous, skeletal, gastrointestinal, pulmonary, cardiac, other, extraskeletal, muscle, and global. The MITAX assesses disease activity in the same organs or systems and is based on the principle of the physician's intent-to-treat analysis (33); each organ or system is graded from A to E depending on the level of disease activity and therapy administered to the patient. The final preliminary core set measure 7) health-related quality of life was assessed via the parent's version of the Child Health Questionnaire (CHQ) (30,34). Briefly, the CHQ includes 15 subscales and 2 summary measures, the physical health score (PhS) and the psychosocial health score (PsS). Higher scores in the scales indicate better health-related quality of life. The parent's versions of both the C-HAQ and the CHQ have been translated and validated in all the languages of the participating countries (30).

Validation procedures. Validation of the core set measures was conducted with the use of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group filter for outcome measures in rheumatology (35,36). The feasibility or practicality of the measures was determined by addressing the issues of brevity, simplicity, ease of scoring, and percentage of missing values. Face and content validity were based on the results of the previous consensus conference (16). Responsiveness was examined by determining the ability of each variable to detect clinically important change between baseline and 6 months, and was measured using the standardized response mean (SRM). The SRM was calculated as the absolute mean change in score divided by the SD of that score; 95% confidence intervals (95% CIs) were also provided (37,38). An SRM value <0.5 is considered a small effect, values between ≥ 0.5 and <0.8 represent a moderate effect, and values ≥ 0.8 represent a large effect (39,40). The SRM is calculated in the patients who improved or did not improve using the physician's judgment of response to therapy as an external marker of change as described below.

Discriminative ability was assessed by evaluating the ability to discriminate patients who experienced improvement from those who did not, based on physician's and parent's judgment. Physicians and parents were asked to judge whether the patient's disease had improved, was stable, or had worsened at the current assessment compared with the baseline evaluation. In order to make the physician's evaluation of disease activity independent from the physician's evaluation of response to therapy, the evaluations where done by 2 observers each one of whom was blinded to the assessment done by the other. Patients who were judged as improving were compared with those who were judged as not improving (i.e., disease remained stable or worsened) by *t*-test or the Mann-Whitney U test, as appropriate. Moreover, the level of concordance between physicians and parents in the evaluation of response to therapy was assessed with the kappa statistic (41), using the threshold proposed by Landis and Koch (42).

Convergent construct validity, which is a form of validation that seeks to examine whether the construct in question is related to other measures in a manner consistent with a priori prediction, was also investigated. As a surrogate measure, we chose the physician's global assessment of the patient's overall disease activity by Spearman's rank correlation (where a value of >0.7 was considered high, a value of $0.4-0.7$ was moderate, and a value of <0.4 was low). We predicted that correlation of the underlying construct of response to therapy with the surrogate gold standard measure would be in the moderate range, and thus would provide a different perspective and avoid redundancy. The issue of colinearity (or redundancy) of variables was investigated by means of Spearman's correlation coefficient; a coefficient ≥ 0.7 was considered to represent evidence of collinearity.

The internal consistency of the various scales was determined by Cronbach's alpha (43) on values at baseline visit, with the following cutoffs: <0.6 = poor, $0.6-0.64$ = slight, $0.65-0.69$ = fair, $0.7-0.79$ = moderate, $0.8-0.89$ = substantial, and >0.9 = almost perfect. We anticipated that a slight/fair Cronbach's alpha would be sufficient to demonstrate the internal consistency of the core set demonstrating the ability of the variables of the core set to "hold together" to measure the underlying construct of response to therapy (14).

Finally, the association between the 6 core measures and response to therapy as judged by the attending physician was evaluated through a multivariate logistic regression analysis, after having dichotomized the core set measures according to the best cutoffs obtained from the receiver operating characteristic curve analysis (44). Determination of the best cutoffs for each core set variable will help physicians to decide whether a patient has improved based on the absolute change in that particular measure.

Data were entered in an Access XP database and analyzed by 2 of the authors (NR and AP) with Excel XP (Microsoft, Redmond, WA), *XL*STAT-Pro 6.1.9 software (Addinsoft, Brooklyn, NY), Statistica 6.0 software (StatSoft, Tulsa, OK), and Stata version 7.0 software (Stata, College Station, TX).

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),

Table 1. Descriptive characteristics of the variables*

Variable	Sample size†	Month 0	Month 6	% change (IQR)	SRM (95% CI)
Final core set					
Physician's global assessment of patient's overall disease activity (0–10-cm scale) ↑	268	5.5 (3.5, 7.2)	1 (0.3, 2.6)	−79 (−94, −41.9)	1.6 (1.4–1.8)
Parent's global assessment of patient's overall well-being (0–10-cm scale) ↑	255	5.2 (3, 7.4)	0.9 (0.1, 2.5)	−75.7 (−97.3, −37.7)	1.2 (1.0–1.4)
CMAS (range 0–52) ↓	269	27 (13, 36.3)	46 (37, 50)	53.1 (14.3, 155)	1.4 (1.2–1.5)
DAS (range 0–20) ↑	273	12 (10, 15)	5 (3, 8)	−58.3 (−75, −33.3)	1.7 (1.5–1.9)
C-HAQ disability index (0–3) ↑	261	1.6 (1, 2.5)	0.3 (0, 1)	−75 (−100, −25)	1.3 (1.1–1.4)
CHQ physical summary score (range 40–60) ↓	211	32.6 (23.7, 42.8)	50.2 (40.8, 54.2)	42.3 (9.2, 84.4)	1.0 (0.9–1.2)
Additional measures					
MMT (range 0–80) ↓	263	48 (32, 61)	71 (59.5, 78)	36.8 (11.1, 89.6)	1.2 (0.9–1.4)
MYOACT (range 0–10) ↑	257	2 (1.1, 3)	0.3 (0.1, 0.8)	−83.1 (−94.6, −57.4)	1.3 (1.1–1.5)
MITAX (range 0–63) ↑	258	17 (9, 25)	2 (1, 5)	−84.3 (−93.3, −62.5)	1.2 (1.0–1.3)
Physician's global assessment of extraskeletal disease activity (0–10-cm scale) ↑	271	2.1 (0.4, 5)	0.3 (0, 1.2)	−75 (−96.1, 0)	0.8 (0.7–0.9)
Physician's global assessment of muscle activity (0–10-cm scale) ↑	270	5.2 (3.1, 7.6)	0.6 (0, 2.1)	−85.2 (−100, −50)	1.4 (1.2–1.6)
CHQ psychosocial summary score (range 40–60) ↓	211	45.7 (40, 51.9)	49.9 (44.6, 54.8)	6.3 (−2.6, 22.3)	0.5 (0.3–0.6)
Parent's global assessment of child's pain (0–10-cm scale) ↑	256	3.2 (0.8, 5.9)	0.2 (0, 1.4)	−83.1 (−100, −8.9)	0.9 (0.7–1.0)
Creatine kinase (0–150 units/liter) ↑	263	254 (76, 1,407)	47.4 (21.6, 9)	−84.5 (−96.8, −21.8)	0.5 (0.4–0.5)
Lactate dehydrogenase (50–150 units/liter) ↑	249	239 (167, 414)	138 (106, 180)	−43 (−65, −15.9)	0.5 (0.3–0.7)
Aldolase (0–6 units/liter) ↑	119	11.6 (6.9, 22.3)	4.7 (3.1, 6.9)	−60.2 (−83.6, −29.4)	0.4 (0.0–0.6)
Aspartate aminotransferase (0–35 units/liter) ↑	248	61.9 (31.5, 135)	22 (15.9, 30)	−60.4 (−85.1, −28.9)	0.5 (0.4–0.6)
Alanine aminotransferase (0–35 units/liter) ↑	256	37.5 (17.5, 80)	16.4 (9.1, 24.5)	−61.7 (−85.7, −9.6)	0.5 (0.4–0.6)

* Except where indicated otherwise, values are the median (interquartile range). SRM is reported for the subgroup of patients who responded to treatment according to the physician's evaluation of response to therapy as an external marker of change (see text for details). ↑ indicates that a higher score for that variable denotes worse disease activity; ↓ indicates that a lower score denotes worse disease activity. IQR = interquartile range; SRM = standardized response mean; 95% CI = 95% confidence interval; CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; C-HAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire; MMT = manual muscle strength testing; MYOACT = Myositis Disease Activity Assessment Visual Analog Scales; MITAX = Myositis Intent-to-Treat Activity Index, A-E version.
† Number of patients for whom both baseline and 6-month evaluations were available.

Latvia (n = 3), Mexico (n = 3), The 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).

Of the 294 patients enrolled, 19 were excluded from the study; 9 of these patients had polymyositis without cutaneous manifestations, 1 patient was later diagnosed as having muscular dystrophy, and 9 patients were lost to followup. Of the 275 (94%) patients who completed both the baseline and 6-month assessments, 168 (61%) were female and 107 (39%) male; the median age at disease onset was 7.2 years (interquartile range [IQR] 4.3, 10.2), and the median disease duration at baseline was 0.6 years (IQR 0.2, 2.1).

With regard to treatment at baseline assessment, 191 (69%) patients were newly started with pulse or oral corticosteroid therapy, 38 (14%) had begun therapy with new immunosuppressive drugs, and 30 (11%) patients had their dosages of previous therapies increased. A subgroup of 111 (40%) patients received newly started corticosteroids in combination with newly started immunosuppressive drugs.

Feasibility and responsiveness. Table 1 shows the characteristics of each clinical variable. The frequency of missing data was uniformly <10%, with the exception of CHQ (19%) and aldolase (36%), demonstrating that all variables had excellent feasibility. At baseline, patients had, on average, a high level of disease activity, as shown by the high median values of the physician's and parent's global assessment and that of the DAS, and by the low median values of both the CMAS and the MMT. The SRM calculated for the subgroup of patients who responded to treatment are shown in Table 1. Good responsiveness to clinical change (SRM ≥0.8) was demonstrated by the 2 global disease activity tools (with the DAS being superior to both the MITAX and the MYOACT), the physician's and parent's global assessment, the CMAS, the MMT, the physician's global assessment of muscle activity, the C-HAQ, the physical summary score of the health-related quality of life tool (CHQ PhS), and the parent's global assessment of the child's pain. All other variables showed moderate re-

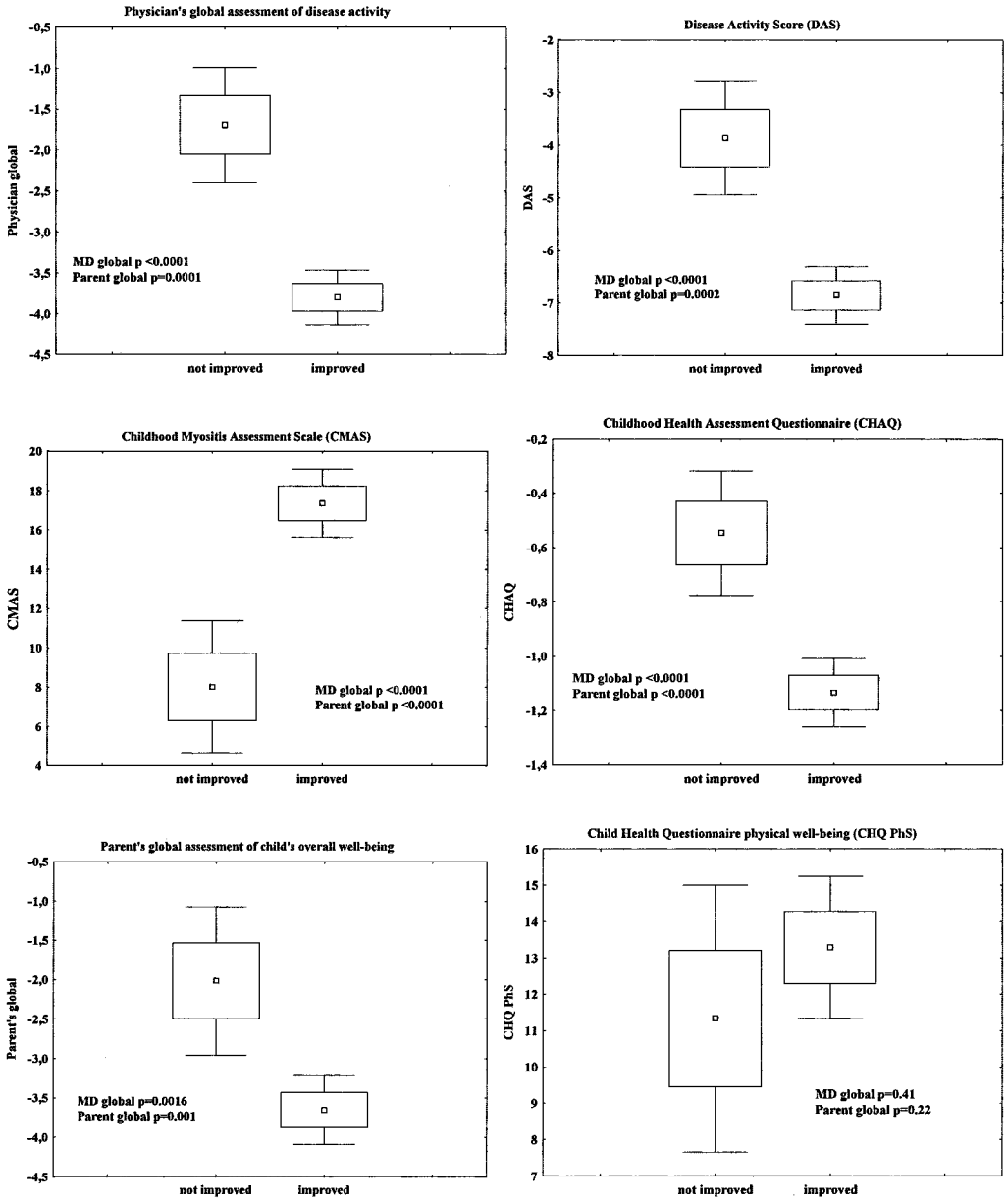

Figure 1. Ability of the variables (mean score changes) included in the core set to discriminate between patients who improved versus patients who did not improve according to the physician's and the parent's evaluation after 6 months of therapy. Data are presented as box plots, where the squares inside the boxes represent the mean, and the line outside the boxes the 95% confidence interval. *P* values refer to the discriminant ability of the variables according to the physician's evaluation and to the parent's evaluation of response to therapy. MD = physician.

sponsiveness, with the exception of the CK whose SRM was small. An important decrease in responsiveness was observed when the SRM was calculated in the subgroup of patients who did not respond to treatment (data not shown).

Taken together, these results did not show a major advantage for any of the additional variables over the variables included in the preliminary core set (16). However, due to the superior responsiveness to clinically important change (and minor skewness) demonstrated by the DAS as compared with the MYOACT and the MITAX, the DAS was selected for use instead of the 2 latter tools; moreover, the DAS was the only index that uses the entire range of possible scores (range 0–20; median score at baseline 12). Furthermore, since, of the 2 summary scales of the CHQ (PhS and PsS), only the PhS yielded significant results in previous analyses, we used only the CHQ PhS as a measure of health-related quality of life in subsequent evaluations.

Discriminant validity. Figure 1 shows the 6 variables included in the final core set, which demonstrated signif-

Table 2. Construct validity for the variables included in the final core set, by Spearman's correlation matrix*

Variable	Physician's global assessment	CMAS	DAS	C-HAQ	Parent's global assessment
CMAS	−0.61				
DAS	0.60	−0.54			
C-HAQ	0.57	−0.71	0.52		
Parent's global assessment of patient's overall well-being	0.51	−0.56	0.42	0.65	
CHQ physical summary score	−0.46	0.61	−0.42	−0.73	−0.58

* Correlations for the absolute change in score (value at month 6 minus value at month 0) were performed and were expected to be in the moderate range (0.4–0.7). A Spearman's coefficient of ≥0.7 was considered to represent evidence of redundancy. CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; C-HAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire.

icant ability (with the exception of the CHQ PhS) in discriminating patients who were improved or not improved at 6 months based on the physician's or parent's assessment of the child's response to therapy. Other variables that were able to show a statistically significant discriminant ability were the MMT, the parents' rating of child's pain, the MITAX (but only for the parent's evaluation), the physician's global assessment of extraskeletal disease activity, the physician's global assessment of muscle activity, 6 of the 8 subscales of the C-HAQ, and 4 of the 15 subscales of the CHQ (data not shown). All the other variables, including the muscle enzymes, the MYOACT, and the MITAX (only for the physician's evaluation), did not show significant discriminant validity. Notably, concordance between physicians and parents in the evaluation of response to therapy was substantial ($\kappa = 0.73$ [95% CI 0.63–0.83]).

Construct validity and redundancy. Table 2 shows Spearman's correlation coefficients for the baseline-to-6-month change in the final core set variables. This analysis was carried out to assess both the construct validity and the colinearity (or redundancy). As expected, the correlation with the physician's global assessment of the patient's overall disease activity was in the moderate range ($r = \pm 0.4$ to ± 0.6) for all variables demonstrating that the final 6 core set variables have good convergent construct validity. There was no redundancy between the core set variables (Spearman's correlation coefficient <0.7), except for the CMAS and the C-HAQ, which revealed some degree of colinearity ($r = -0.71$). In spite of this finding, it was decided to retain both parameters in the core set because it was felt that they assess largely different constructs, with the first being a measure of muscle strength and endurance and the second a measure of functional ability (16). The high correlation of the CMAs with the MMT ($r = 0.77$), and their similar responsiveness, suggested that they are interchangeable measures of muscle strength.

Table 3. Internal consistency of the variables in the final core set*

Variable	Cronbach's α
Physician's global assessment of patient's overall disease activity	0.60
Parent's global assessment of patient's overall well-being	0.60
CMAS	0.49
DAS	0.59
C-HAQ	0.63
CHQ physical summary score	0.56

* Values shown are Cronbach's alpha when the individual variable is removed. The performance of the final core set, including all 6 variables, was 0.63. CMAS = Childhood Myositis Assessment Scale; DAS = Disease Activity Score; C-HAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire.

Internal consistency. As shown in Table 3, assessment of the baseline values of the 6 variables combined yielded

Table 4. Logistic regression model to predict improvement according to the physician's evaluation*

Variable	OR (95% CI)	*P*, likelihood ratio test
Physician's global assessment of patient's overall disease activity	3.4 (1.5–7.4)	0.002
DAS	3 (1.4–6.5)	0.005
Parent's global assessment of patient's overall well-being	1.7 (0.7–4)	0.23
CMAS	1.2 (0.5–3)	0.71
C-HAQ	0.8 (0.3–2)	0.57
CHQ physical summary score (>17.3)	1 (0.3–3.2)	0.996

* Predictions were based on absolute change of the variables included in the final core set. Variables were dichotomized according to the best cutoffs obtained from the receiver operating characteristics (ROC) curve analysis. The area under the ROC curve of the model was equal to 0.74. The best cutoffs were as follows: for the physician's global assessment of patient's overall disease activity, ≤ −2.4; for the Disease Activity Score (DAS), ≤ −5; for the parent's global assessment of patient's overall well-being, ≤ −3.7; for the Childhood Myositis Assessment Scale (CMAS), >5; for the Childhood Health Assessment Questionnaire (C-HAQ), ≤ −1; for the Child Health Questionnaire (CHQ) physical summary score, >17.3. OR = odds ratio; 95% CI = 95% confidence interval.

Table 5. Domains and suggested variables included in the final core set for the evaluation of response to therapy in juvenile DM*

Domain	Suggested variable(s)
Physician's global assessment of patient's overall disease activity	10-cm VAS
Muscle strength	CMAS (or MMT)
Global juvenile DM disease activity tool	DAS (or MYOACT or MITAX)
Parent's global assessment of patient's overall well-being	10-cm VAS
Functional ability assessment	C-HAQ
Health-related quality of life assessment	CHQ physical summary score

* Juvenile DM = juvenile dermatomyositis; VAS = visual analog scale; CMAS = Childhood Myositis Assessment Scale; MMT = manual muscle testing; DAS = Disease Activity Score; MYOACT = Myositis Disease Activity Assessment Visual Analog Scales; MITAX = Myositis Intent-to-Treat Activity Index, A-E version; C-HAQ = Childhood Health Assessment Questionnaire; CHQ = Child Health Questionnaire.

a Cronbach's alpha of 0.63, meaning, as expected, that there was slight internal consistency. When we added the muscle enzyme CK, Cronbach's alpha fell to 0.006, suggesting that the inclusion of this measure in the core set leads to a disruption of its internal consistency.

Association between changes in each of the 6 core set measures and overall outcome. In the final logistic regression model (Table 4), the physician's global assessment of the patient's overall disease activity and the DAS appeared to be the strongest predictors of response to therapy, whereas the predictive ability of the other 4 variables did not reach statistical significance. The table also shows the absolute change cutoffs that should be observed in each variable of the core set in order to classify the patient as a responder to a given therapy; for example the 6-month absolute change in the physician's global assessment of the patient's overall disease activity should be ≤ -2.4 on a scale of 0–10 cm.

Selection of the final core set. Taken together, the results of the validation analyses showed that the final core set for the evaluation of response to therapy in juvenile DM has excellent psychometric properties. Table 5 presents the 6 domains and the related suggested variables used to measure each domain that is included in the final core set. In future studies, it is recommended that the results for muscle enzymes also be reported, but only for descriptive purposes.

DISCUSSION

In this report, we present the final validated PRINTO/American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) core set of clinical measures for the assessment of response to therapy in patients with juvenile DM assessed through a large, prospective data collection and a comprehensive validation process that closely mimicked the design of a clinical trial. The selected variables were shown to be feasible and to have good construct validity, discriminative ability, and internal consistency; furthermore, they were not redundant, were responsive to clinically important change, and they were strongly associated with treatment outcome. The validation of the core set is a fundamental step in the process of developing a definition of improvement in juvenile DM.

Recently, the IMACS group independently undertook a similar effort, which led to the development of a core set of outcome measures and preliminary definitions of improvement in adult and juvenile IIM (7,8,32). Although the overall structure of the PRINTO/ACR/EULAR core set and IMACS core set domains is remarkably similar (which ensures convergent validity to the process followed by the 2 networks), there are some important differences. First, serum muscle enzymes, which are part of the IMACS core set and were included in the preliminary PRINTO/ACR/EULAR core set (16), have been removed from the final PRINTO/ACR/EULAR core set as a result of their poor statistical performance in the validation analyses (see below). Second, health-related quality of life assessment has been selected as a distinct core set domain by the PRINTO/ACR/EULAR group, whereas the IMACS investigators did not incorporate it in the core set, although they recommended this measure be included in therapeutic trials of patients with IIM. The PRINTO/ACR/EULAR core set is given a unique strength by the validation process reported herein, which enabled the evidence-based scrutiny and selection of the candidate variables through the analysis of a large, prospectively collected patient sample.

The PRINTO/ACR/EULAR core set was designed to be robust enough to cover all disease phenotypes of juvenile DM, focusing on the central features of the physician's subjective estimation of the level of disease activity, muscle strength, global disease activity scoring, parent's global assessment of the patient's overall well-being, functional ability, and the health-related quality of life. It should be kept in mind, however, that the recommended variables are not more than a minimal core set, and that investigators can measure as many other variables as they deem appropriate for the major hypothesis that is being tested.

In recent years, there has been increasing collaborative effort to pool expertise in order to devise composite activity indices for a standardized clinical assessment of juvenile DM (5,6). Two global disease activity measures for juvenile DM are currently available, the DAS (31) and the MDAA (32). Compared with the MDAA, the DAS revealed superior responsiveness to clinically important change, minor skewness, and better ability to use the entire range of possible scores and for these reasons, was included in the core set.

Evaluation of the extent and severity of muscle inflammation is of major importance in assessing disease activity and response to therapy in juvenile DM patients. Muscle strength is the primary clinical measure used to assess muscle disease. The MMT (23) is the most widely used method for muscle strength measurement in therapeutic trials; however, the most popular muscle function tool in

children with juvenile DM is the CMAS (20–22), which evaluates a combination of muscle strength, muscle function, and endurance. We found that the MMT and CMAS had similar responsiveness and a certain degree of redundancy. The latter finding led us to suggest that the 2 tools can be used interchangeably for the evaluation of muscle strength. Potential advantages of the MMT are its brevity and forwardness, whereas the CMAS may be easier to use with younger children. The good statistical performances yielded by the measure of physical function (the C-HAQ) are in keeping with those obtained in previous studies in juvenile DM patients (45). Keeping with the results of the initial consensus conference (16) the final PRINTO/ACR/EULAR core set maintained the distinction between the measures to evaluate muscle strength (CMAS or MMT) and functional ability (by C-HAQ) despite a certain degree of redundancy between the 3 tools. This distinction is another difference from the IMACS core set where only the MMT is presented as a measure of muscle strength while the CMAS or the C-HAQ are presented as measures of functional ability.

The measurement of serum levels of muscle-derived enzymes has long been used as an indicator of myositis activity in the clinical management of patients with juvenile DM. High levels of enzymes may help to differentiate active disease from disease remission or muscle damage, in which their levels are usually normal or near normal. However, it is well known that many patients have no muscle enzyme elevation at the time of diagnosis (24–28). Furthermore, CK levels and other muscle enzymes often do not correlate with measures of muscle strength, with CK levels improving without a correspondent improvement in muscle function. The imperfect correlation of serum muscle enzymes with myositis activity was confirmed in our analyses, which revealed that all enzymes were only moderately or poorly responsive to change in disease activity over time. Furthermore, the inclusion of CK levels into the core set of variables led to a marked decrease in internal consistency. For this reason, it was decided to exclude serum muscle enzymes from the final core set.

Health-related quality of life has been increasingly recognized as an important domain to be included in therapeutic trials and observational studies of patients with juvenile DM because it addresses aspects of disease that are not fully captured by other endpoints (5,6). Therefore, the assessment of health-related quality of life was incorporated in the juvenile DM core set as a separate domain. We found that the physical scale of the CHQ had better evaluative properties than the psychosocial scale, which may be partially explained by the observation that patients with juvenile DM have greater impairment in physical than in psychosocial well-being (46).

Our study has certain limitations, which include the fact that it was not conducted in the context of a real clinical trial, and that the use of corticosteroids or immunosuppressive drugs as intervention therapy was not standardized and might have led to changes in the level of disease activity much greater than those that would be expected in trials of novel immunosuppressive or biologic agents. We did not investigate the role of imaging modalities (i.e., magnetic resonance imaging [47–49] or muscle ultrasound) both of which are increasingly used to assess muscle disease activity; however, the magnetic resonance imaging is costly and not readily available in many centers, and muscle ultrasound has not yet been sufficiently standardized. Moreover, the use of somewhat similar dimensions for the evaluation of the physician's global assessment of disease activity and physician's evaluation of response to therapy might have introduced some bias despite the required separation between the role of the 2 physicians. The main strength of the study is the large amount of prospectively collected data, which ensured an evidence-based initial validation analysis. To our knowledge, this is the first time that clinical measures of juvenile DM have been tested longitudinally for their statistical performance, individually and as a group.

In conclusion, we have presented the validated PRINTO/ACR/EULAR core set of outcome domains for the evaluation of response to therapy in juvenile DM, which will constitute the basis for creating a definition of improvement to be used in randomized clinical trials. This will allow improved assessment of efficacy of new therapeutic agents or regimens, with greater validity and comprehensiveness.

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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.

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