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ORIGINAL ARTICLE

Development and Validation of a Composite Disease Activity Score for Juvenile Idiopathic Arthritis

ALESSANDRO CONSOLARO,[1] NICOLINO RUPERTO,[2] ANNA BAZSO,[2] ANGELA PISTORIO,[2] SILVIA MAGNI-MANZONI,[3] GIOVANNI FILOCAMO,[2] CLARA MALATTIA,[2] STEFANIA VIOLA,[2] ALBERTO MARTINI,[4] AND ANGELO RAVELLI,[4] FOR THE PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION

Objective. **To develop and validate a composite disease activity score for juvenile idiopathic arthritis (JIA), the Juvenile Arthritis Disease Activity Score (JADAS).**

Methods. **The JADAS includes 4 measures: physician global assessment of disease activity, parent/patient global assessment of well-being, active joint count, and erythrocyte sedimentation rate. These variables are part of the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30), Pedi 50, and Pedi 70 criteria for improvement. Validation analyses were conducted on >4,500 patients and included assessment of construct validity, discriminant validity, and responsiveness to change. Three versions of the JADAS were tested based on 71-joint (range 0–101), 27-joint (range 0–57), or 10-joint (range 0–40) counts. Statistical performances of the JADAS were compared with those of 2 rheumatoid arthritis composite scores, the Disease Activity Score in 28 joints (DAS28) and the Clinical Disease Activity Index (CDAI).**

Results. **The JADAS demonstrated good construct validity, yielding strong correlations with JIA activity measures not included in the score and moderate correlations with the Childhood Health Assessment Questionnaire. Correlations obtained for the 3 JADAS versions were comparable, but superior to those yielded by the DAS28 and CDAI. The area under the curve of the JADAS predicted long-term disease outcome, measured as radiographic progression over 3 years. In 2 clinical trials, the JADAS discriminated well between ACR Pedi 30, Pedi 50, and Pedi 70 response and revealed strong responsiveness to clinical change.**

Conclusion. **The JADAS was found to be a valid instrument for assessment of disease activity in JIA and is potentially applicable in standard clinical care, observational studies, and clinical trials.**

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease with a widely variable clinical course and outcome (1). Evaluation of disease activity is a fundamental component of the clinical assessment of children with JIA because persistently active disease plays a major role in causing joint damage and physical functional disability. Furthermore, measurement of the level of disease activity over time is important in assessing the effectiveness of antirheumatic drugs in clinical trials and in monitoring the patient's course in daily care.

A variety of instruments are available for measuring disease activity in JIA, including global assessment scales, pain measures, various types of joint counts, functional ability questionnaires, acute-phase reactants, and even more general measures, such as hemoglobin level, white blood cell count, platelet count, serum immunoglobulin

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[1]Alessandro Consolaro, MD: Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genoa, and the Università degli Studi di Verona, Verona, Italy; [2]Nicolino Ruperto, MD, MPH, Anna Bazso, MD, Angela Pistorio, MD, PhD, Giovanni Filocamo, MD, Clara Malattia, MD, Stefania Viola, MD: Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genoa, Italy; [3]Silvia Magni-Manzoni, MD: Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia, Italy; [4]Alberto Martini, MD, Angelo Ravelli, MD: Istituto di Recovero e Cura a Carattere Scientifico G. Gaslini, Genoa, and the Università degli Studi di Genova, Genoa, Italy.

Drs. Consolaro and Ruperto contributed equally to this work.

Address correspondence to Angelo Ravelli, MD, Pediatria II, Istituto G. Gaslini, Largo G. Gaslini 5, 16147 Genoa, Italy. E-mail: angeloravelli@ospedale-gaslini.ge.it.

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level, body weight, and requirement for increasing medications. However, due to the high variability in the clinical presentation and course of JIA, no single measure can reliably capture disease activity in all patients. Conversely, evaluation of all measures individually is associated with methodologic and statistical problems, especially when these measures are employed as end points in clinical trials. Measures of disease activity, which assess the signs and symptoms related to inflammation, should be separated from measures of disease severity, such as those that assess functional impairment and structural joint damage.

To achieve a more rational and standardized approach, a core set of variables to be used in JIA disease activity assessment has been established by the American College of Rheumatology (ACR) (2). This core set is composed of the following 6 measures: physician global assessment of disease activity, parent/patient global assessment of well-being, active joint count, restricted joint count, functional assessment, and a laboratory measure of inflammation. Using this core set, a definition of improvement in JIA was developed (the ACR Pediatric 30 [Pedi 30], Pedi 50, and Pedi 70 criteria for improvement) (2).

The ACR Pedi 30, Pedi 50, and Pedi 70 response criteria emphasize change in disease state and, therefore, are a tool for assessment of clinically relevant improvement in disease activity. However, the nature of their calculation does not enable the measurement of actual disease activity or the comparison of one patient's absolute response with that of another patient's. Furthermore, they do not allow discernment of whether one group of patients has more active disease than another group.

Similar considerations in adult rheumatology conferred a rationale for pooling individual measures of disease activity into composite scores. These tools were aimed to quantify the absolute level of disease activity by providing one summary number on a continuous scale. A number of such scores have been developed for rheumatoid arthritis (RA), including the Disease Activity Score (3), the Disease Activity Score in 28 joints (DAS28) (4), the Simplified Disease Activity Index (5), and the Clinical Disease Activity Index (CDAI) (6). These measures have the advantage of creating better consistency in disease activity evaluation across physicians, of allowing patients to better understand the meaning of disease activity by providing a single score number, and of reducing the sample size requirement in clinical trials (7). Composite disease activity scores can be used in the assessment of therapeutic efficacy in clinical trials and in monitoring disease activity in individual patients in standard clinical practice.

At present, such measures do not exist for JIA. For this reason, the purpose of the present study was to develop and validate a composite disease activity score for JIA, called the Juvenile Arthritis Disease Activity Score (JADAS).

PATIENTS AND METHODS

Development of the JADAS. The composite disease activity score for JIA was devised by a panel of 9 pediatric rheumatologists (AC, NR, AB, SM-M, GF, CM, SV, AM, and AR) with 2 to >20 years of clinical experience in the field, who reached consensus on the individual measures to be included in the score. Investigators were asked to base their choice on their clinical experience and on a review of the pertinent literature. All investigators agreed that the components of the JADAS should be selected from the 6 variables included in the ACR Pedi 30, Pedi 50, and Pedi 70 core set (2). However, it was felt that 2 of the 6 variables, restricted joint count and functional assessment, were not suited for inclusion in the JADAS because they are affected by disease damage (functional or structural) (8). Functional status assessment was not included because it has been shown to be relatively insensitive to change in JIA (9–12). The parent global assessment was also found to reflect functional damage, particularly in the later stages of illness (8). However, it was believed important to include this parameter in order to incorporate parents' perception of disease activity. The physician global assessment was included because it represents the most responsive measure in JIA (9–11).

Other measures were also considered. Pain rating was discarded because it is reflected in the parent/patient global assessment. The swollen and tender joint counts were not included because they are highly correlated with active joint count (8,13,14). Although health-related quality of life (HRQOL) is largely driven by the disease process, it is influenced by many external factors. Therefore, HRQOL-related questionnaires were not thought to measure disease activity reliably.

The final version of the JADAS that was agreed upon by the study panel included the following 4 measures: physician global assessment of disease activity, measured on a 10-cm visual analog scale (VAS) where 0 = no activity and 10 = maximum activity; parent/patient global assessment of well-being, measured on a 10-cm VAS where 0 = very well and 10 = very poor; count of joints with active disease; and erythrocyte sedimentation rate (ESR). The choice of ESR instead of C-reactive protein (CRP) level was dictated by its availability as a sole acute-phase reactant in most study data sets (see below).

To substantiate that the combination of these variables truly measures a single construct, e.g., disease activity, principal component analysis was performed on the 6 core set variables plus the parent assessment of pain and the swollen and tender joint counts. This analysis was done on a HRQOL study and on a methotrexate (MTX) trial (see below). Two factors with eigenvalues >1 and a cumulative percentage of explained variance of 66% were identified. The first factor included the joint counts, and the second factor included the physician's and parent's subjective assessments, the Childhood Health Assessment Questionnaire (C-HAQ), and ESR (data not shown). These findings supported the choice of the selected variables as measures of disease activity.

Based on a previous analysis that showed that the 27-joint reduced count is a good surrogate for the whole joint count in JIA (15), it was decided, due to its greater feasibility, to incorporate this reduced count (named the JADAS-27) in the JADAS. The JADAS-27 includes the following joints: cervical spine, elbows, wrists, meta-

Table 1. Composition and theoretical range of the composite disease activity scores tested in the study*

	JADAS-71	JADAS-27	JADAS-10	DAS28	CDAI
Physician global assessment	0–10-cm VAS	0–10-cm VAS	0–10-cm VAS	–	0–10-cm VAS
Parent/patient global assessment	0–10-cm VAS	0–10-cm VAS	0–10-cm VAS	0–1.40-mm VAS	0–10-cm VAS
Active joint count	Simple, 0–71 joints	Simple, 0–27 joints	Simple, 0–10 joints†	–	–
Swollen joint count (range)	–	–	–	28 joints, square-root-transformed (0–1.48)	Simple, 0–28 joints
Tender joint count (range)	–	–	–	28 joints, square-root-transformed (0–2.96)	Simple, 0–28 joints
Acute-phase reactant (range)	Normalized ESR (0–10)‡	Normalized ESR (0–10)‡	Normalized ESR (0–10)‡	Log-transformed ESR (0.49–3.22)	–
Score range	0–101	0–57	0–40	0.49–9.07	0–76

* JADAS-71 = Juvenile Arthritis Disease Activity Score in 71 joints; DAS28 = Disease Activity Score in 28 joints; CDAI = Clinical Disease Activity Index; VAS = visual analog scale; ESR = erythrocyte sedimentation rate.
† Up to 10 joints, irrespective of their type, censored at 10.
‡ According to the formula: (value in mm/hour −20)/10, where values <20 mm/hour are converted to 0, and values >120 mm/hour are converted to 120.

carpophalangeal joints (from first to third), proximal interphalangeal joints, hips, knees, and ankles. Two additional versions of the JADAS, one including the entire 71 joints (JADAS-71) and one including a 10-joint reduced count (JADAS-10; based on the count of any involved joint, irrespective of its type, up to a maximum of 10 joints), were tested in the validation analyses.

The ESR value was normalized to a 0–10 scale according to the following formula:

$$\frac{\text{ESR(mm/hour)} - 20}{10}$$

Before making the calculation, ESR values <20 mm/hour were converted to 0 and ESR values >120 mm/hour were converted to 120.

The JADAS was calculated as the simple linear sum of the scores of its 4 components, which yields a global score of 0–57, 0–101, and 0–40 for the JADAS-27, JADAS-71, and JADAS-10, respectively.

The study protocol was approved by the Ethics Committee of the Istituto G. Gaslini, Genoa, Italy.

Study data sets. Four samples composed of patients meeting the International League of Associations for Rheumatology criteria for JIA (16) were used to validate the JADAS. The first was a cross-sectional sample of 434 unselected patients who underwent a clinic visit in the authors' units between 2002 and 2007. The second sample was also cross-sectional and included 3,324 patients enrolled in a study on HRQOL by the Paediatric Rheumatology International Trials Organisation (17). The third sample was composed of 595 patients with polyarthritis included in a controlled trial that compared intermediate versus higher doses of MTX (18). The fourth sample comprised 225 patients with oligoarthritis or polyarthritis included in a controlled trial that compared meloxicam with naproxen (19). The unselected clinic patients included all JIA subtypes, but patients with rheumatoid factor (RF)–positive polyarthritis were excluded from the MTX trial, and patients with psoriatic arthritis and enthesitis-related arthritis were excluded from the HRQOL study, the MTX trial, and the meloxicam/naproxen trial.

Validation procedures. Validation of the JADAS was based on evaluation of construct validity, discriminant validity, and responsiveness to change. In all analyses, the statistical performances of the JADAS were compared with those of 2 RA disease activity scores: the DAS28 (4) and the CDAI (6). The individual elements included in the composite scores were examined and their theoretical ranges are presented in Table 1. In all scores, the parent global rating was used as a substitute for the patient global assessment, because the latter measure was available for only a few observations.

Construct validity is a form of validation that examines whether the construct in question, in this case the JADAS, is related to other measures in a manner consistent with a priori prediction. Given that the JADAS was devised to measure JIA activity, it was predicted that its correlation with swollen and tender joint counts would be high, because both are measures of closely related constructs. Correlations with parent rating of pain intensity, C-HAQ score (20), and restricted joint count were predicted to be moderate because these measures combine the effect of both disease activity and damage. Correlations with CRP level were also predicted to be moderate because it is known that clinical measures of disease activity correlate only moderately with acute-phase reactants (8,14). It was anticipated that correlations for the JADAS would be similar to those for the DAS28 and the CDAI because these scores measure the same construct.

Construct validity of the JADAS was further evaluated by examining its correlation with radiographic progression. Sufficient clinical data were available for 60 of the 103 patients included in a recent study on the validation of adapted versions of the Sharp/van der Heijde score in patients with JIA (21) who had wrist/hand radiographs performed at first observation and after 3 years. Correlation between the area under the curve of the JADAS and the observed changes in radiographic score over 3 years was

Table 2. Main demographic and clinical features of the 4 patient samples*

	Clinic patients (n = 434)		HRQOL study (n = 3,324)		Methotrexate trial† (n = 595)		Meloxicam/naproxen trial† (n = 225)	
	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)	No.	Median (IQR)
Age at disease onset, years	434	3.4 (1.9–6.0)	3,114	5.2 (2.6–8.7)	592	4.4 (2.0–8.5)	–	5.0 (2–8)
Age at study visit, years	434	7.2 (3.9–11.2)	3,141	10.6 (7.2–14)	595	7.8 (4.2–11.3)	225	8.0 (5–12)
Disease duration, years	434	2 (0.8–5.4)	3,115	3.8 (1.6–6.7)	592	1.1 (0.4–3.4)	–	1.8 (0.5–4)
Swollen joint count	425	2 (0–3)	2,768	1 (0–4)	594	7 (4–13)	225	3 (2–6)
Tender joint count	425	1 (0–3)	2,768	1 (0–3)	594	7 (4–14)	225	3 (2–6)
Restricted joint count	425	1 (0–3)	2,768	2 (0–7)	594	8 (5–14)	225	3 (2–7)
Active joint count	425	2 (0–4)	2,768	2 (0–5)	594	9 (6–16)	225	4 (2–7)
Physician global assessment‡	400	3.4 (0.0–7.3)	2,758	1.8 (0.4–3.9)	590	5.1 (3.7–6.6)	225	3.4 (2.2–5.3)
Parent global assessment‡	225	1 (0.0–3.7)	2,853	1.4 (0.1–4.2)	591	4.5 (2.2–6.3)	225	3.5 (2.2–5.2)
Parent pain assessment‡	225	1 (0.0–3.7)	2,849	1.4 (0.1–4.1)	589	4.5 (2.4–6.9)	–	–
C-HAQ score§	232	0.1 (0.0–0.3)	2,857	0.38 (0.0–1.12)	592	1.25 (0.62–1.75)	225	0.62 (0.25–1.25)
ESR, mm/hour¶	306	15 (9–38)	2,450	20 (10–38)	581	40 (22–62)	218	12.0 (6.6–25)
CRP level, mg/dl#	227	0.5 (0.4–1.5)	–	–	–	–	–	–
JADAS-71	207	4.5 (0.6–12.5)	2,424	7.5 (2.9–15.3)	573	22.1 (16.1–29.9)	218	11.9 (8.3–18.2)
JADAS-27	207	4.5 (0.5–11.2)	2,424	7.2 (2.8–14.3)	573	20.4 (15.1–26.5)	218	11.5 (8.0–17.5)
JADAS-10	207	4.5 (0.6–12.5)	2,424	7.5 (2.9–14.7)	573	19.7 (15.8–24.5)	218	11.9 (8.3–17.3)
DAS28	211	2.5 (1.8–3.7)	2,438	3.0 (2.0–4.1)	577	5.0 (4.3–5.8)	218	3.5 (2.8–4.3)
CDAI score	221	5.0 (1.0–12.6)	2,725	6.2 (2.1–12.6)	587	19.4 (14.3–29.7)	225	11.4 (8.0–17.9)

* HRQOL = health-related quality of life; IQR = interquartile range; C-HAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein. See Table 1 for additional definitions.
† At baseline.
‡ Range 0 (best) to 10 (worst).
§ Range 0 (best) to 3 (worst).
¶ Normal at <20 mm/hour.
# Normal <0.46 mg/dl.

computed. Only the JADAS-71 and JADAS-10 could be assessed because the type of joints involved over time was not known. All correlations were calculated using Spearman's rank statistics. Correlations were considered high, moderate, or strong at >0.7, 0.4–0.7, or <0.4, respectively (25).

For the assessment of discriminant validity, we characterized patients by their degree of improvement according to the ACR Pedi 30, Pedi 50, and Pedi 70 response criteria (2) in the 2 clinical trials. Patients were divided by their maximum level of improvement at 6 and 3 months, respectively, into 4 mutually exclusive groups: nonresponders, Pedi 30 responders, Pedi 50 responders, and Pedi 70 responders. Using one-way analysis of variance, we analyzed whether changes in JADAS were greater in ACR Pedi 50 and Pedi 70 response groups, and whether these differences were statistically significant at a group level. Comparisons of quantitative variables among groups were made by means of the nonparametric analysis of variance (the Kruskal-Wallis nonparametric test); Dunn's test was chosen as a posteriori test to assess the statistical significance of differences between pairs of patient groups.

The responsiveness to change of the disease activity scores was assessed by computing the standardized response mean (SRM) in the 2 clinical trials. The SRM was calculated as the mean baseline-to-end point change in score divided by the SD of the individual's change in score (23). In line with Cohen (24), the threshold levels for SRM were defined as follows: ≥0.20 = small, ≥0.50 = moderate, and ≥0.80 = good. Distribution of composite scores was examined by assessing their skewness and kurtosis. In the case of normal distribution, the value of these parameters will be 0.

All statistical tests were 2-sided, and *P* values less than 0.05 were considered statistically significant. The statistical packages used were Statistica (StatSoft, Tulsa, OK) and Stata, version 7 (Stata Corporation, College Station, TX).

RESULTS

The main demographic and clinical features of the 4 patient samples are shown in Table 2.

Construct validity. *Correlations on cross-sectional data.* The Spearman's correlations between the JIA clinical measures that were not incorporated in the scores of the cross-sectional patient samples and the 3 JADAS versions, the DAS28, and the CDAI are presented in Table 3. Overall, correlations were better for clinic patients and HRQOL study patients than they were for clinical trial patients. As predicted, JADAS correlations with joint counts were in the moderate-to-high range, whereas correlations with parent pain rating, C-HAQ score, and CRP level were moderate. Also as predicted, restricted joint count was correlated with JADAS at a lower level as compared with swollen joint count. Correlations yielded by the JADAS-71 were similar to those yielded by the versions based on reduced joint counts, with the exception of the poorer correlations between the JADAS-10 and swollen, tender, and restricted joint counts in the MTX trial. In general,

Table 3. Spearman's correlation between the composite disease activity scores and the juvenile idiopathic arthritis outcome measures not included in the scores on cross-sectional data*

	JADAS-71	JADAS-27	JADAS-10	DAS28	CDAI
Clinic patients					
Parent pain assessment	0.73	0.72	0.73	0.61	0.64
C-HAQ score	0.50	0.50	0.51	0.51	0.46
Swollen joint count	0.82	0.81	0.82	–	–
Tender joint count	0.73	0.71	0.73	–	–
Restricted joint count	0.78	0.76	0.77	0.71	0.72
CRP level	0.52	0.53	0.52	0.54	0.46
HRQOL study					
Parent pain assessment	0.60	0.61	0.62	0.55	0.61
C-HAQ score	0.56	0.56	0.57	0.52	0.56
Swollen joint count	0.77	0.75	0.76	–	–
Tender joint count	0.69	0.67	0.69	–	–
Restricted joint count	0.64	0.62	0.62	0.59	0.60
Methotrexate trial†					
Parent pain assessment	0.38	0.41	0.53	0.38	0.31
C-HAQ score	0.47	0.50	0.52	0.44	0.42
Swollen joint count	0.68	0.63	0.44	–	–
Tender joint count	0.64	0.57	0.50	–	–
Restricted joint count	0.61	0.56	0.40	0.49	0.63
Meloxicam/naproxen trial†					
Parent pain assessment	–	–	–		
C-HAQ score	0.34	0.33	0.34	0.28	0.36
Swollen joint count	0.67	0.65	0.63	–	–
Tender joint count	0.66	0.62	0.63	–	–
Restricted joint count	0.66	0.64	0.63	0.57	0.65

* C-HAQ = Childhood Health Assessment Questionnaire; CRP = C-reactive protein; HRQOL = health-related quality of life. See Table 1 for additional definitions.
† At baseline.

correlations yielded by the DAS28 and CDAI were lower than those yielded by the JADAS.

Changes in JADAS in relation to changes in C-HAQ, DAS28, and CDAI scores. The Spearman's correlations observed for score changes in clinical trials are shown in Table 4. As expected, JADAS correlations with C-HAQ scores were moderate, whereas JADAS correlations with DAS28 and CDAI scores were high. Correlations were comparable across JADAS versions, except for correlations between the JADAS-10 and the CDAI, which were lower than those yielded by the JADAS-71 and JADAS-27. Correlations with C-HAQ scores were higher for the JADAS than for the DAS28 and CDAI.

Relationship with radiographic outcome. Spearman's correlation between the area under the curve of JADAS disease activity and the changes in adapted total Sharp/van der Heijde score over 3 years were moderate ($r_s = 0.47$ for the JADAS-71 and $r_s = 0.50$ for the JADAS-10). Both correlations were highly significant ($P < 0.001$), therefore demonstrating that the composite score predicts radiographic progression.

Discriminant validity: changes in JADAS in relation to ACR Pedi 30, Pedi 50, and Pedi 70 response. In the MTX trial, the percentages of nonresponders and ACR Pedi 30, Pedi 50, and Pedi 70 responders at 6 months were 27.7%,

Table 4. Spearman's correlation between the baseline–end point changes in the composite disease activity scores and C-HAQ scores in the MTX and meloxicam/naproxen trials*

Trial (no. patients)	JADAS-71	JADAS-27	JADAS-10	DAS28	CDAI
MTX (490)					
C-HAQ score	0.46	0.50	0.51	0.44	0.44
DAS28	0.78	0.80	0.79	–	–
CDAI	0.88	0.86	0.72	–	–
Meloxicam/naproxen trial (204)					
C-HAQ score	0.44	0.43	0.45	0.35	0.39
DAS28	0.74	0.74	0.70	–	–
CDAI	0.87	0.86	0.75	–	–

* C-HAQ = Childhood Health Assessment Questionnaire; MTX = methotrexate. See Table 1 for additional definitions.

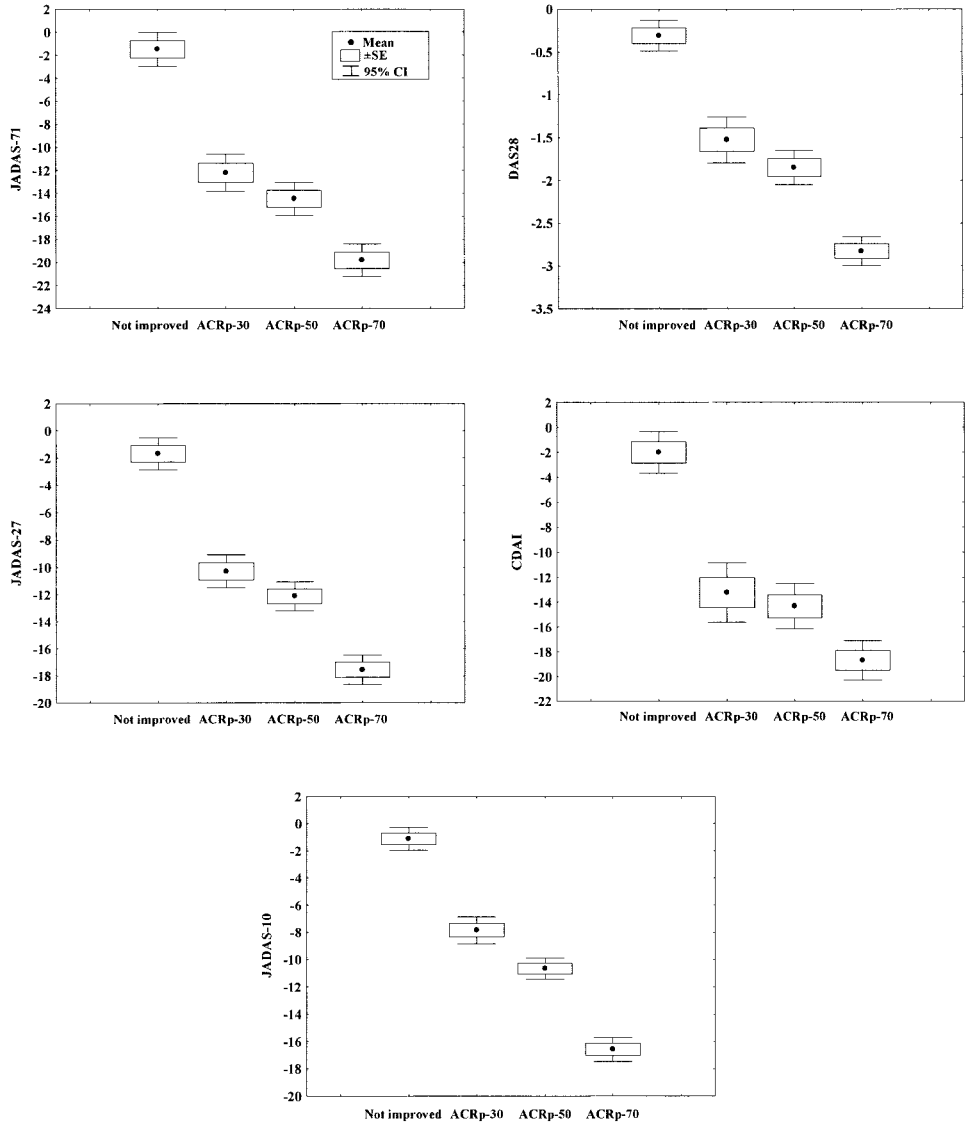

Figure 1. Comparison of the ability of the composite disease activity scores to discriminate between different levels of American College of Rheumatology (ACR) Pediatric 30 (ACRp-30), ACRp-50, and ACRp-70 response in the methotrexate trial (n = 490). Boxplots are the means, SEs, and 95% confidence intervals (95% CIs) of composite disease activity score values in patients grouped by ACRp response category. The number of nonresponders and ACR 30%, 50%, and 70% responders were 136, 58, 111, and 185, respectively. JADAS-71 = Juvenile Arthritis Disease Activity Score in 71 joints; DAS28 = Disease Activity Score in 28 joints; CDAI = Clinical Disease Activity Index.

11.8%, 22.7%, and 37.8%, respectively. In the meloxicam/naproxen trial, the percentages were 38.3%, 13.3%, 17.3%, and 31.2%, respectively. The changes in the 3 JADAS versions and in the DAS28 and CDAI in relation to the ACR Pedi 30, Pedi 50, and Pedi 70 response in the MTX trial are shown in Figure 1. All JADAS versions discriminated significantly between the ACR Pedi 30, Pedi 50, and Pedi 70, and their discriminant validity was comparable with that of the DAS28 and CDAI. However, Dunn's post hoc test revealed that only the JADAS-10 discriminated between ACR Pedi 30 and ACR Pedi 50 responses ($P < 0.05$). Similar findings were obtained for the meloxicam/naproxen trial (data not shown).

Responsiveness to clinical change and score distribution. The SRMs for the 3 JADAS versions, the DAS28, and the CDAI in the MTX and meloxicam/naproxen trials are shown in Table 5. All composite scores revealed strong responsiveness to clinical change, with SRM values above 0.8. The responsiveness of JADAS and RA composite scores was comparable, although the JADAS-10 proved slightly superior. However, a subanalysis of the nonresponders in the MTX and meloxicam/naproxen trials showed that the JADAS-27 was slightly more responsive than the JADAS-10 (data not shown). The JADAS-10 and DAS28 revealed the best score distribution, with values of skewness and kurtosis close to

Table 5. Responsiveness of composite disease activity scores in the methotrexate and meloxicam/naproxen trials*

	Methotrexate trial (n = 490)	Meloxicam/naproxen trial (n = 204)
JADAS-71	1.17 (1.05–1.29)	0.89 (0.67–1.07)
JADAS-27	1.27 (1.14–1.39)	0.98 (0.84–1.11)
JADAS-10	1.29 (1.18–1.41)	1.04 (0.90–1.18)
DAS28	1.23 (1.12–1.34)	0.89 (0.75–1.03)
CDAI	1.06 (0.95–1.17)	0.93 (0.76–1.07)

* Values are the standardized response mean (95% confidence interval). See Table 1 for definitions.

zero in most data sets, followed by the JADAS-27 (data not shown).

DISCUSSION

This study describes the development and validation of a new composite disease activity score for JIA. This score combines information from 2 physician-centered measures (physician global assessment and active joint count), 1 parent/patient-centered measure (parent/patient global assessment), and 1 acute-phase reactant (ESR) into a continuous measure of inflammation.

The clinical measures included in the JADAS are part of the ACR Pedi 30, Pedi 50, and Pedi 70 core set of outcome variables (2). These variables were identified through a comprehensive statistical and consensus formation process, which involved a large number of international experts, and are universally recognized as the central measures of disease activity in all phenotypes of JIA. The choice of the 4 variables to be incorporated into the JADAS was based on the review of the existing literature and agreed upon by a panel of 9 pediatric rheumatologists with a wide range of clinical experience. Inclusion of the selected variables was supported by principal component analysis. Altogether, these processes ensure the face and content validity of the instrument.

The score of the JADAS results from the arithmetic sum of the scores of each individual component, which makes its calculation simple and quick. The physician and parent/patient global assessments are both measured on a 0–10-cm VAS. To reduce the potential that joint count might dominate the index, the 27-joint reduced count was selected for inclusion in the JADAS. This count has been found to be a valid surrogate for the whole joint count in JIA (15). However, because the active joint count is of primary importance in the definition of JIA activity, the validity of the JADAS-27 was compared with that of 2 additional versions: the whole 71-joint count and the 10-joint reduced count. To avoid giving the acute-phase reactant an excessive weight in the index, the ESR value was converted to a 0–10 scale with a simple formula that does not require a computer or calculator.

To provide an adequate strength to the validation process, the construct validity, discriminant validity, and responsiveness to clinical change of the JADAS were assessed using 4 patient samples including >4,500 patients from several different countries. These patients are likely to be representative of the whole spectrum of JIA severity.

The JADAS demonstrated good construct validity in cross-sectional samples by yielding strong correlations with JIA activity measures not included in the score, such as the swollen and tender joint counts, and moderate correlation with the C-HAQ. Correlations were similar across patient samples, which indicate that the index may be robust enough to cover all phenotypes of JIA and levels of disease activity. Correlations obtained for the 3 JADAS versions were comparable, but superior to those yielded by the DAS28 and CDAI. This suggests that the RA composite scores are not equally as reliable as JADAS in capturing the level of disease activity in children with JIA. In the 2 clinical trials, the change in JADAS was moderately correlated with the change in C-HAQ score, and strongly correlated with the changes in DAS28 and CDAI score. Correlations of RA composite scores with C-HAQ scores were lower than those with the JADAS. Further evidence of construct validity of the JADAS was provided by the demonstration that its area under the curve predicted disease outcome, measured as radiographic progression over 3 years. This led us to establish that the JADAS has good predictive validity.

The JADAS discriminated well between ACR Pedi 30, Pedi 50, and Pedi 70 response in the 2 clinical trials; that is, proportionately greater changes in the JADAS corresponded with nonresponse and ACR Pedi 30, Pedi 50, and Pedi 70 response levels. The discriminative ability of the JADAS was comparable with that of the DAS28 and CDAI. Responsiveness of the JADAS to change in the 2 clinical trials was good (all SRM values >0.8) and was similar to that of the DAS28 and CDAI.

This study has some potential limitations. In validation analyses, only the parent global assessment could be assessed because the patient self-reporting was not available. However, using only parents' proxy reports instead of both parents' and patients' self-reports fails to capture the fact that parents and children may differ in their perception of health (25,26). Other parent-centered measures, such as functional assessment, could be equally important in the measurement of JIA activity. We found that versions of the JADAS including the C-HAQ (27) or the physical function scale of the Child Health Questionnaire (28) instead of the parent global assessment performed similarly to the original JADAS (data not shown).

We did not attempt to create different composite scores for the various subsets of JIA. However, although the score was designed to be robust enough to cover all categories of JIA, a thorough assessment of disease activity in children with systemic JIA requires quantification of extraarticular manifestations, particularly fever and rash (29). The study results might not be extrapolated to the categories of RF-positive polyarthritis, psoriatic arthritis, and enthesitis-related arthritis, which were excluded from 3 of 4 patient samples. A subanalysis in MTX trial patients revealed that the statistical performance of the 3 JADAS versions was comparable in the main JIA subtypes (systemic, RF-negative polyarthritis, and extended oligoarthritis; data not shown).

Another study limitation is the omission of assessment

of ocular disease, which is an important feature of disease activity in JIA. However, the study panel did not include this clinical manifestation because no standardized grading of its activity is available. We recognize that 3 of the 4 data sets were also used for the development and validation of reduced joint counts (15), raising the possibility of bias. However, the statistical performance of 3 of the 5 joint counts investigated in that study has been revaluated with additional analyses. Although the JADAS revealed satisfactory discriminant validity, this property needs to be further scrutinized by determining the minimum clinically important difference. Statistical performances of the JADAS-27 were comparable with those provided by the JADAS-71. However, assessment of 27 joints is more feasible and less tedious than evaluation of 71 joints. The simplest, 10-joint reduced count revealed the best discriminating validity, responsiveness (though not in nonresponder patients), and distribution, but had a somewhat poorer construct validity. The greater responsiveness of this joint count may be explained by most JIA patients having few joints involved. Use of this reduced count, which does not enable a precise assessment of joint disease and may limit the ability to detect new joint involvement over time, is advised only for use in retrospective studies, when the total number of involved joints is known, but no information on the individual affected joints is available. We could only test ESR because CRP values were available only in 1 database. However, CRP is a direct measure of the acute-phase response and is less confounded by other factors, including intercurrent infections, compared with ESR. Therefore, a version of the JADAS including CRP levels instead of ESR is worth testing in the future.

In conclusion, we have developed a new composite disease activity score for JIA, which is based on the simple arithmetic sum of 4 clinical measures. The instrument was found to be feasible and to possess both face and content validity; furthermore, it exhibited good construct validity, discriminant validity, and responsiveness to clinically important change in a large population of patients. By documenting these key measurement properties, we have shown that the JADAS is a valid instrument for the assessment of disease activity in JIA and is, therefore, potentially applicable in standard clinical care, observational studies, and clinical trials.

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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. Ravelli 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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