Responsiveness of clinical measures to flare of disease activity in juvenile idiopathic arthritis

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Abstract

Objective

To compare the responsiveness of clinical measures in the assessment of disease flare in patients with juvenile idiopathic arthritis (JIA).

Methods

The clinical records of all consecutive patients with JIAwho were diagnosed between 1995 and 2000 were retrospectively reviewed. In each patient, all visits made during follow-up were analyzed and those meeting the criteria for disease flare were recorded. The definition of flare was based on the therapeutic alterations made by the attending physician. Responsiveness of JIA clinical measures to relevant increase in disease activity (a flare) was evaluated by assessing the score change of each measure from a visit made 6 (± 3) months before a flare and the flare visit. Responsiveness statistics included the standardized response mean (SRM) and the effect size (ES).

Results

A total of 115 patients, who were followed for 0.5 to 6.2 years (mean 2.8 years), were studied. During follow-up, 51 patients (44%) experienced 1 or more disease flares, with the total number of flares being 75. Strong responsiveness (ES and SRM ≥ 0.8) to increase in disease activity was demonstrated by the physician's and parent's global assessments, the global articular severity score, and the morning stiffness. The active, swollen and painful joint counts, the swelling, pain on motion/tenderness and limited range of motion (LROM) scores, and the erythrocyte sedimentation rate revealed moderate responsiveness (ES and SRM ≥ 0.5). The poorest performances (ES and/or SRM < 0.5) were provided by the parent's assessment of pain, the functional ability tool, the number of joints with LROM, the LROM score, the C-reactive protein, the white blood cell and platelet count, and the hemoglobin level.

Conclusion

Our analysis suggests that the swollen or painful joint counts are better suited than the count of joints with LROM for the assessment of disease flare in patients with JIA.

Key words

Juvenile idiopathic arthritis, disease flares, responsiveness.

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous condition, which clinical course is frequently characterized by variations in the degree of inflammation (1). These fluctuations manifest clinically as alternations between instances of acute worsening of symptoms and phases of relative quiescence. Exacerbation of disease activity, which is commonly referred to as disease flare, is an important clinical event because it may indicate a poorer patient prognosis (2) and generally prompts the clinician to intensify the treatment regimen. To define important decrease in disease activity, criteria for clinical improvement in JIA have been developed, which are based on 6 core response variables (CRV) (3). These criteria, which have recently been adopted by the American College of Rheumatology (ACR) and are now called ACR Pediatric 30, have been used in non - controlled and controlled clinical trials to measure the effects of treatment interventions in patients with JIA(4-6). Using the CRV and the data of a randomized controlled trial of etanercept (4), preliminary criteria for defining disease flare in patients with polyarticular-course JIAhave recently been created (7). However, it is unknown whether the CRV are superior to the other clinical and laboratory measures of JIA activity in detecting a disease flare. Indeed, the relative responsiveness (8-10) of JIA response variables to clinically important increases in disease activity has not been well documented. The purpose of the present study was to compare the responsiveness of the CRV to relevant increase in disease activity (a flare) to that of the clinical and laboratory measures of JIA activity not included in the CRV.

Patients and methods

The clinical records of all consecutive patients who were diagnosed as having JIAby the revised International League for Associations of Rheumatology (ILAR) criteria (11) at the Department of Pediatrics of the University of Pavia, Italy between January, 1995 and December, 2000 and were followed for a minimum of 6 months were retrospectively reviewed. In each patient, all visits made during follow-up were analyzed and those meeting the criteria for disease flare were recorded. A disease flare was defined as the presence of at least 1 of the following 5 criteria: 1) new start, restart or dose increase ≥ 0.2 mg/kg/day of prednisone; 2) new start, restart or dose increase ≥ 5 mg/m^2/ week of methotrexate (MTX) or, in patients with enthesitis related arthritis, new start or restart of sulfasalazine; 3) association to MTX or sulfasalazine of a second-line drug, including biologic agents (combination therapy); 4) new start or restart of nonsteroidal antiinflammatory drug (NSAID) therapy; 5) execution of intraarticular corticosteroid injection. For any flare to be defined as such, the above criteria had to be associated with an increase in the physician's global assessment of overall disease activity (MD global) on a 10-cm visual analogue scale (VAS) (0=no activity; 10=maximum activity) ≥ 3 cm with respect to the previous clinical evaluation or, if the MD global was not available, with a confirmation of a disease flare, based on the review of clinical data, made by an experienced pediatric rheumatologist (AR or SV). Exacerbations of systemic manifestations in patients with systemic JIA or ocular flares in patients with chronic anterior uveitis which were not associated with exacerbation of articular symptoms were excluded from the analysis.

Responsiveness of clinical measures of JIAactivity to relevant increases in disease activity (a flare) was evaluated by assessing the score change of each measure from a visit made 6 (± 3) months before flare and the flare visit. It was assumed that the disease activity of the patients would, on average, significantly increase from the pre-flare to the flare visit. If a patient had received more than one clinic visits in the pre-flare period, the visit closer to the flare was chosen. Pre-flare visits meeting the criteria for disease flare were excluded form the analysis. The following clinical variables were recorded at the pre-flare and flare visit: MD global, assessed as above indicated; parent's global assessment of the child's overall well being (Parent global) on a 10-cm VAS

(0=very well; 10=very poor); parent's assessment of the the child's pain (Parent pain) on a 10-cm VAS (0=no pain; 10=very severe pain); Childhood Health Assessment Questionnaire (CHAQ) disability index (0=no disability, 3= maximum disability), Italian version (12); number of joints with active arthritis (defined as the number of joints with swelling or, if no swelling was present, as the number of joints with pain on motion/tenderness + limited range of motion, LROM); number of swollen joints; swelling score; number of joints with pain on motion/tenderness; pain on motion/tenderness score; number of joints with LROM; LROM score; number of joints with LROM + pain on motion/tenderness; overall articular severity score; morning stiffness in minutes; erythrocyte sedimentation rate (Westergren method); C reactive protein (nephelometry), white blood cell count, hemoglobin level, and platelet count. In each patient, the articular indices were assessed in a total of 67 joints (those joints that are included in the normal clinical evaluation) by a single examiner (AR or SV). The swelling and pain on motion/tenderness scores were graded from 0 to 3 and the LROM score from 0 to 4, and the overall articular severity score was calculated as the sum of the severity ratings obtained for the scores of pain on motion/tenderness, swelling, and LROM, as previously reported (13). We were facilitated in gathering joint involvement at specific time points because we routinely perform and record on standardized sheets a detailed joint assessment in each patient at each clinic visit. The laboratory tests were available for most, though not all, clinic visits.

Statistics

The responsiveness of clinical measures of JIAactivity in detecting a relevant change (a flare) was calculated by using the pre-flare evaluation as baseline and the flare evaluation as final time point. Responsiveness statistics included the standardized response mean (SRM) and the effect size (ES). The SRM was calculated as the mean change in score divided by the standard deviation (SD) of individuals' change in score (14), and the ES as the mean change in score divided by the SD of individuals' baseline score (15). Ninety-five per cent confidence intervals (95% CI) for the SRM were calculated using a jackknife procedure to obtain the approximate distribution of the estimate in the sample (16). All n patients were used to compute the estimate of SRM for each clinical variable. Next, the i-th subject was removed and new values were computed: m_i, s_i and d_i; i = 1,…., n; and corresponding "pseudo-values" were calculated as $di^* = n \times d - (n-1) \times d_i$. Then δ was estimated by the sample mean of the pseudo-values as:

$$\delta^* = \frac{1}{n} \sum_{i=1}^{n} d_i^*$$

and the variance of δ^* was estimated by:

$$V(\delta^*) = \frac{1}{n} \times \left\{ \frac{1}{n-1} \times \sum_{i=1}^{n} \left(d_i^* - \delta^* \right)^2 \right\}.$$

Confidence intervals (95%) based on the t distribution were calculated as $d^* \pm t_{0.05}$ radq ($V(\delta^*)$), where $t_{0.05}$ is the 97.5 percentile of a t distribution with n-1 degrees of freedom. According to Cohen (17), the threshold levels for SRM and ES were defined as follows: ≥0.20=small, ≥0.50= moderate, ≥ 0.80 = strong. The statistical package "Statistica for Windows" (release 6, StatSoft) was used to perform all the analyses.

Results

A total of 115 patients, whose main clinical features are reported in Table I, were included in the study. During the follow-up period of 0.5 to 6.2 years (mean 2.8 years), 51 patients (44%) experienced 1 or more disease flares, with the total number of flares being 75. Thirty-six patients (31%) had only 1 flare and 15 patients (13%) had more than 1 flare. The frequency of flare per patient per year of follow-up was 0.24. The frequency of flare by JIAcategory was 58% in the systemic, 33% in the polyarticular, 39% in the persistent oligoarticular, 64% in the extended oligoarticular, and 30% in the enthesitis related/psoriatic.

Table II shows the frequency of the criteria used to define the disease flare. Among the therapeutic criteria, the most frequent (75%) was the execution of ≥1 intraarticular corticosteroid injection, reflecting the greater proportion of patients with oligoarticular JIA, which is the subtype in which this therapeutic procedure is most commonly performed. The second and third criteria, in order of frequency, were the new start or restart of NSAID therapy (39%)

Table I. Clinical features of the 115 study patients.

	N	%	Mean	SD
Males/Females	24/91	21/79		
JIAsubtype				
Systemic	12	10		
Polyarticular	15 #	13		
Oligoarticular	78	68		
Persistent	56	49		
Extended	22	19		
ERA/Psoriatic arthritis	10	9		
Age at onset (years)			4.9	3.6
Age at diagnosis (years)			8.9	4.1
Time lag onset-diagnosis (months)			13.9	24.5
Disease duration § (months)			48.0	32.1
Follow-up duration £ (months)			34.1	18.9
No. patients with no flares	64	56		
No patients with ≥ 1 flares	51	44		
No patients with 1 flare	35	30		
No patients with > 1 flares	16	14		

2 rheumatoid factor positive; ERA: enthesitis related arthritis; § from onset to last observation; £ from diagnosis to last observation.

Table II. Frequency of the flare criteria in the 75 instances of disease flare.

	N	%
Therapeutic criteria		
New start, restart or dose increase of prednisone	12	16
New start, restart or dose increase of methotrexate	17	23
Start of combination therapy	9	12
New start or restart of NSAID therapy	29	39
Execution of ≥ 1 intraarticular corticosteroid injection	56	75
Physician's criteria		
Increase of physician's global assessment ≥ 3 cm #	33	44
Confirmation by an experienced clinician $	42	56

NSAID: non-steroidal antiinflammatory drug; #: on a 10 cm visual analogue scale (0=no disease activity; 10=maximum activity); $: obtained in cases where the physician's global assessment was not available and the physician's assessment had to be generated retrospectively.

Table III. Responsiveness of clinical measures of JIAactivity in the detection of a disease flare.

Variable	N	Mean value (SD) at baseline	Mean change (SD)	Effect size	SRM	95% CI
Subjective variables						
Physician global assessment #	20	1.8 (2.3)	5.4 (2.6)	2.32	2.07	0.67-3.17
Parent global assessment #	17	1.8 (1.6)	1.5 (2.0)	0.97	0.80	0.19-1.28
Parent pain assessment #	17	1.2 (2.1)	1.0 (2.5)	0.47	0.40	0-0.98
Functional assessment tool						
CHAQ score §	18	0.2 (0.5)	0.2 (0.4)	0.50	0.60	0.25-0.96
Articular indices						
No active joints	32	3.2 (4.8)	4.5 (7.5)	0.94	0.60	0.25-0.81
No swollen joints	32	1.9 (3.5)	2.6 (4.3)	0.75	0.60	0.01-0.92
Swelling score	32	2.0 (3.2)	4.5 (6.4)	1.41	0.71	0-1.25
No joints with pain/tenderness	32	1.7 (3.0)	4.8 (7.3)	1.61	0.67	0.44-0.87
Pain/tenderness score	32	1.90 (3.7)	7.0 (10.9)	1.90	0.64	0.44-0.82
No joints with LROM	32	2.9 (4.9)	3.7 (9.6)	0.76	0.39	0-0.72
LROM score	32	4.1 (7.3)	3.3 (5.7)	0.44	0.57	0.09-0.82
No joints with LROM + POM/TD	32	1.5 (2.5)	3.1 (5.2)	1.24	0.59	0.41-0.74
Global articular severity score	32	8.4 (12.0)	14.4 (18.7)	1.19	0.81	0.42-0.99
Morning stiffness (min.)	21	10.2 (17.2)	32.1 (38.2)	1.86	0.84	0.42-1.14
Laboratory indicators of inflammation						
ESR (mm/h)	43	18.9 (14.7)	17.1 (24.9)	1.16	0.69	0.47-0.87
C-reactive protein (mg/dl)	35	1.8 (3.5)	3.1 (6.8)	0.87	0.45	0.29-0.59
WBC count (x 10^3/ml)	45	9.3 (4.6)	1.1 (4.2)	0.24	0.26	0.02-0.50
Hemoglobin (g/dl)	46	11.7 (1.5)	-0.4 (1.0)	0.26	0.42	0.04-0.76
Platelet count (x 10^3/ml)	46	360.1 (119.4)	51.3 (96.9)	0.43	0.53	0.36-0.69

SD: standard deviation; # on a 10 cm visual analogue scale (0=best; 10=worst); CHAQ: Childhood Health Assessment Questionnaire; § on a 3 point scale (0=best; 3=worst); POM: pain on motion; TD: tenderness; LROM: limited range of motion; ESR: erythrocyte sedimentation rate; WBC: white blood cells.

and the new start, restart or dose increase of MTX. The 2 physician's (confirmatory) criteria were applied in roughly half of the patients each.

Table III illustrates for each measure of JIA activity, when available, the mean baseline value, the mean change from the pre-flare to the flare visit, and the results of responsiveness statistics. The only measures that revealed both good (≥ 0.8) ES and SRM were the physician (by definition, because it was one of the flare criteria) and parent global assessments, the global articular severity score, and the morning stiffness. Moderate responsiveness (ES and SRM ≥ 0.5) was shown by the CHAQ, the active, swollen and painful joint counts, the count of joints with LROM + pain on motion/tenderness, the swelling and pain/tenderness scores, and the ESR. The Parent pain, the number of joints with LROM, the LROM score, the CRP, the hemoglobin level, and the WBC and platelet counts were the less responsive measures (ES and/or SRM < 0.5).

Discussion

At present, there is no universally accepted definition of disease flare in JIA. We created a definition that was based on the retrospective evaluation of the therapeutic alterations made by the attending physician and was believed to be able to cover all JIA categories. Because the occurrence of a major exacerbation of symptoms generally prompts the physician to make a modification of the therapeutic regimen aimed to achieve the disease control, we assumed that a patient could have been considered as having a disease flare in case of start or restart or dose increase of prednisone, start or restart or dose increase of second-line drug therapy, start of combination therapy, start or restart of NSAID therapy, or execution of intraarticular corticosteroid therapy. This definition was strengthened by the addition of 2 clinical criteria, 1 of which had to be met: a ≥ 3 cm increase in the MD global as compared to the previous clinical evaluation or, in the case of its absence, a confirmation of the diagnosis of disease flare by an experienced pediatric rheumatologist. Notably, it is unlikely that differences in the therapeutic choices between the attending physicians have biased the results because in our group these choices have been quite consistent during the study period.

Recently, Brunner *et al*. (7) proposed preliminary criteria for defining disease flare in patients with polyarticular-course JIA, which were based on the CRV for JIA (3). The 6 CRV are the physician's global assessment of overall disease activity, the parent's global assessment of the child's overall well being, the score of a functional assessment tool, the number of joints with active arthritis, the number of joints with LROM, and a laboratory marker

of inflammation. The best suitable definition of flare identified was "at least 40% deterioration of 2 of the 6 CRV without concomitant improvement of more than 1 of the remaining CRV by more than 30%". In our study, we were interested in comparing, using data obtained in daily clinical practice, the responsiveness to a relevant increase in disease activity (a flare) of the CRV to that of the conventional measures of JIA activity not included in the CRV. We found that the MD global (by definition, because it was one of the flare criteria), the Parent global, the CHAQ, the number of active joints, and the ESR had good-to-moderate responsiveness. At variance, the number joints with swelling and with pain on motion/ tenderness appeared to be more responsive than the number of joints with LROM, suggesting that the 2 former articular variables are better suited for the assessment of disease flare in JIA.

We must acknowledge the study limitations, which include the retrospective nature of the data collection, the relatively small size of some JIA subtypes, the heterogeneity of the flare criteria, the fact that some patients could not be evaluated at the time of a flare, and the lack of the clinical and laboratory measures of JIA activity in a number of flare and/or pre-flare visits. Furthermore, the fact that study assessments were done by 2 experienced rheumatologists from a single center might have affected the high responsiveness of swollen joint count. Indeed, the assessment of joint swelling has been found in previous research to have poor inter-rater reliability (18).

In conclusion, although our responsiveness analysis supports the use of the CRV in the assessment of disease flare in JIA, it suggests that the swollen or painful joint counts are more responsive to relevant increases in disease activity than the count of joints with LROM. The relative performance of candidate variables in the assessment of disease flare should be further explored in larger prospective studies.

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