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Disease control and health-related quality of life in JIA

Michael Seid, PhD[*], **Lisa Opipari, PhD**, **Bin Huang, PhD**, **Hermine I. Brunner, MD MSc**, and **Daniel J. Lovell, MD, MPH**

Cincinnati Children's Hospital Medical Center

Abstract

Objective—To examine variability in health related quality of life (HRQOL) among children with JIA experiencing no or minimal clinical symptoms, and for a subgroup with polyarticular JIA treated with biologics for 12 months.

Method—Defined three samples, using database of patients, 2–18 years, with JIA (n = 524; patient visits (PV) = 2,354): 1) visits (PV = 2155) with no or minimal clinical symptoms on at least one of four measures (active joint count, pain, physician global disease rating, Child Health Assessment Questionnaire); 2) visits (PV = 941) with no or minimal symptoms on all four measures; and 3) children (n=31) with polyarticular JIA treated with biologics for 12 months. HRQOL was measured using the Pediatric Quality of Life Inventory (PedsQL) and percentage of patients with sub-optimal HRQOL was determined.

Results—Suboptimal HRQOL, by self-report, occurred in 20.6% (pv=362) of visits with at least one indicator of minimal symptoms and in 7.9% (pv=64) of visits with all four measures indicating minimal symptoms (25.7% (pv=519) and 10.7% (pv=95) by parent report). For children with polyarticular JIA treated for 12 months with biologics, 25.9% (n=7) by self-report (35.7% (n=10) by parent report) were in the suboptimal range of HRQOL.

Conclusion—A substantial percentage of patients with JIA who report no or mild clinical symptoms experience suboptimal HRQOL. This is true also for polyarticular JIA patients treated with biologics for 12 months. Although disease activity and clinical symptoms are related to HRQOL, considerable unexplained variation in HRQOL exists. HRQOL needs to be assessed independently regardless of clinical status.

Juvenile idiopathic arthritis (JIA), the most common childhood rheumatic disease, has no cure and can result in significant pain and physical disability. Because JIA can influence virtually all aspects of a child's and his or her family's life, clinicians and researchers increasingly recognize that improved health-related quality of life (HRQOL) is a key treatment goal for JIA (1). The importance of HRQOL as a primary outcome is echoed by the Federal Food and Drug Administration (2), the Centers for Disease Control and Prevention (3), and the World Health Organization (WHO) (4).

HRQOL, at its simplest, refers to how an individual feels about certain aspects of their life with respect to their health or health condition. HRQOL consists, at a minimum, of physical,

[*]Corresponding Author: 3333 Burnet Ave, ML 2021, Cincinnati, OH, 45229-3039; michael.seid@cchmc.org, 513-803-0083, FAX 513-636-4615.

mental, and social health dimensions originally delineated in 1948 by the World Health Organization (4). While researchers have documented worse HRQOL for children with JIA compared to healthy controls (5–7), others have found minimal differences between these groups in psychosocial outcomes such as parental distress, family functioning, social support (8), and HRQOL (9). Despite these equivocal findings, HRQOL is known to be associated with medical variables in children with JIA. Recent studies showed that better self-report (10) and parent proxy-report of child HRQOL (5, 6) is associated with better parent ratings of child functional ability, pain intensity, well-being, physician rating of disease activity and erythrocyte sedimentation rate (ESR). These relationships are in the small- to medium-effect size range (11). While functional ability, physician rating and ESR were related to physical functioning scales of the HRQOL measures, ratings of pain and well-being were related to the psychosocial functioning scales of the HRQOL measures. Given the well-documented lack of concordance between self- and proxy-report in the adult and pediatric literature, (12, 13) it is important to assess both child self-report and parent proxy-report HRQOL whenever possible.

Implicit in the measurement of HRQOL is the notion that medical interventions can affect not only clinical parameters (e.g., pain, joint count) but also more distal outcomes, such as HRQOL. While much research has focused on understanding how biological and physiological variables affect disease outcomes, far less is known about how clinical parameters and therapeutic interventions are related to HRQOL. This knowledge gap is particularly relevant in the context of new biologic therapies used in the treatment of JIA due to potential long-term safety issues (currently unknown) and high cost of the therapies. These new therapies have resulted in statistically significant mean increases (small to medium effect sizes) in HRQOL for adults with rheumatoid arthritis (RA) (14, 15). However, these trials highlight a key issue – substantial unexplained variation in HRQOL outcomes between patients with similar disease control (i.e., dissociation between traditional medical outcomes and HRQOL outcomes). For example, in recent RA clinical trials, the standard deviations for HRQOL within a treatment group is sometimes larger than the average HRQOL improvement and 5–15% of the treatment group actually show a worsening in HRQOL. While biologics represent great potential for improved HRQOL in children with JIA, such improvement is by no means assured.

Given the growing understanding of HRQOL as an important outcome, the traditional focus of therapeutics on medical outcomes, and the relative lack of knowledge regarding how clinical parameters and therapeutic interventions affect HRQOL in children with JIA, there is a need to understand parent and child perceptions of HRQOL for children with minimal symptoms and children treated with biologics. This study addresses this need by describing variability in HRQOL among children with JIA. We hypothesized that while clinical functioning would be correlated with HRQOL (5, 6, 10), significant variation in HRQOL would be found in groups of children with JIA experiencing minimal clinical symptoms, as well as for a subgroup with polyarticular JIA treated with biologics(14, 15).

Patients and Methods

Patients

This study is based on a clinical data base prospectively collected by clinical protocol in the pediatric rheumatology clinic at Cincinnati Children's Hospital Medical Center between 2003 – 2007. All children 2 to 18 years old (n = 524) who presented for evaluation and treatment of JIA and completed the Pediatric Quality of Life Inventory (PedsQL) during their visit (patient visit (PV) = 2,354), were included in the analysis.

We examined HRQOL for three non-exclusive subsets of this database, selected in order to create more homogeneous clinical samples for assessing HRQOL variation. The first subset consisted of visits with a PedsQL™ score at which patients had minimal symptoms on at least one of four clinical characteristics (n = 500; PV = 2155 visits), the second, visits with a PedsQL™ score at which patients had minimal symptoms on all four clinical characteristics (n = 308; PV = 941 visits), and the third, children with polyarticular JIA who had a visit with a PedsQL™ score within 30 days of having been treated with biologic therapies for 12 months (n = 31; PV = 31) irrespective of symptom control. For this last subsample, we determined presence or absence of biological therapy, rather than an ordinal scale based on dose, because studies of TNF inhibitors have shown similar profound effects on disease control in JIA and there are no comparative studies among biologics to support a dose-response relationship (16–18).

Note that these samples are subsets of each other, not unique subsets. To whit: 2155 = PV in which the patient reported minimal symptoms on at least 1 of 4 measures (a subset of the 2354 total PV in the analysis); 941= PV in which patients had minimal symptoms on all 4 measures simultaneously (a subset of the 2155 PV); 402 = PV in which patients had a score of 0 on all 4 measures simultaneously (a subset of the 941 PV); 31 = patients meeting the biologic therapy criteria (a subset of the 524 patients).

Measures

Health Related Quality of Life—HRQOL was measured using the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales (19) and Rheumatology module (7, 20, 21). The PedsQL consists of parallel forms for children (ages 5–18 years) to report on their own HRQOL and for parents of children 2–18 years to report on their child's HRQOL. The PedsQL Generic Core Scales and Rheumatology module have been shown to be reliable, valid, sensitive to disease severity, and responsive to change in JIA (7). We defined optimal HRQOL as a score no less than one minimally clinical important difference (MCID) below the mean of healthy children on the PedsQL Generic Core Total scale. The MCID is the smallest difference in a domain of interest that patients perceive to be beneficial and that would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's care management (22). The PedsQL MCID is 4.4 points (22) (larger than the minimal detectable difference in this sample of 0.90 = (1.96 * sqrt(2) * SEM) (23))and the mean score of healthy children is 83 points (19, 22). Thus, a PedsQL Generic Core Total scale score of below 78.6 is defined as sub-optimal.

Medical variables—Medical variables were collected as part of standard of clinical care. These included disease duration; JIA subtype; Active Joint Count (AJC); patient pain measured using a visual analog scale (0 = no pain, 10 = very severe pain) by patient report or parent proxy (24); physician global assessment of disease activity using a visual analog scale (0 = inactive disease, 10 = very active disease) (25, 26); and physical function, measured using the Childhood Health Assessment Questionnaire (CHAQ) disability index (27, 28). This index is calculated as the unweighted average of 30 questions in 8 domains covering major aspects of daily living over a one-week period and yields a score between 0 (no disability) and 3 (most severe disability).

"Minimal symptoms" was defined as follows: AJC of less than or equal to 2 joints; patient (or parent) pain rating less than or equal to 2; physician global assessment of disease activity less than or equal to 2; and Childhood Health Assessment Questionnaire disability index less than or equal to 0.13 (mild disability)(29).

Statistical Methods

Patient demographic and disease characteristics were summarized on their first visits. Generalized estimating equation (GEE) analyses were conducted to examine the association between clinical characteristics and the PedsQL, taking into account the clustered data structure. All GEE analyses included patient's age, gender, race, ethnicity, age at onset of disease, and duration of disease as covariates. For subsets of patients with minimal symptoms on at least one clinical characteristic and on all four clinical characteristics, the number of patient-visits, number of patients, corresponding PedsQL means and variance between and within patients were reported. In addition, using 78.6 as the cut point, the number and percent of patient-visits and patients falling below optimal level were determined. All analyses were carried out in SAS v9. Analysis of this de-identified data set was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

Results

The sample consisted of 524 children with a total of 2,354 visits. Mean age of entering the study was 10.00 years (SD = 4.67; range = 2 to 18 years). Mean age of diagnosis was 5.53 years (SD = 4.15; range = 0 to 16). The sample was predominantly female (n=387, 73.9%) and white (n=475, 90.5%). Mean disease duration was 4.42 years (SD=4.26) and was categorized into the following subtypes for 524 patients: oligoarticular extended (n = 46,8.8%), oligoarticular persistent (n = 184, 35.1%), polyarticular RF-negative (n = 202, 38.6%), polyarticular RF-positive (n = 27, 5.2%), psoriatic arthritis (n = 2, 0.4%), systemic (n =56, 10.7%), enthesitis-related arthritis (n = 2, 0.4%). Subtypes were missing on 5 patients. The average number of visits per patient (APV) was 4.49 visits per patient. Of PV with at least 1 indicator of minimal symptoms, 1756 self-report and 2020 parent-report PedsQL scores existed. For visits with all 4 measures indicating minimal symptoms, the denominators were 810 and 891 for self- and proxy-report, respectively.

The result of GEE analyses are summarized in Table 1 by type III chi-square statistics and the corresponding p values. After adjusting for patient's age, gender, race, ethnicity, age at

onset of disease and duration of disease, and accounting for the clustering of data with patients, all clinical characteristics have significant effects (p<.001) on PedsQL by both parent and child report. Including all clinical characteristics, all clinical characteristics remained significantly associated with parent report, but only Pain VAS score and CHAQ remain significantly associated with child report of PedsQL.

Suboptimal HRQOL, by self-report, occurred in 20.6% (pv=362) of visits with at least one indicator of minimal symptoms and in 7.9% (pv=64) of visits with all four measures indicating minimal symptoms (25.7% (pv=519) and 10.7% (pv=95) by parent report). Table 2 shows descriptive statistics (Number of patient-visits, Number of patients, Mean, between and within patient variances) and percent of patient-visits and patients below an optimal level of HRQOL (i.e. < 78.6 points) on the PedsQL Generic Core Scales by child self-report and parent-proxy report stratified by four clinical characteristics. As disease functioning worsens, child and parent reported HRQOL also worsens. Even though mean PedsQL scores are in the optimal range for the group as a whole, a substantial proportion of children with minimal symptoms on each characteristic are experiencing scores considered suboptimal. Among all patient-visits when active joint count is 0, 23% (pv=260) of patient-visits and 27% (pv=103) of patients have suboptimal HRQOL based on parent-proxy report, while 18% (pv=181)of patient-visits and 22% (pv=76) of patients have suboptimal HRQOL based on child-self report. Similar results are seen for Pain VAS rating, MD global assessment, and CHAQ. When considering minimal symptoms on all 4 characteristics simultaneously ($0 < AJC \leq 2$, $0 <$ pain rating ≤ 2, $0 <$ physician global assessment ≤ 2 and $0 <$ CHAQ score $\leq .13$), 15% (pv=74) of patient-visits and 19% (pv=43)of patients by the parent proxy-report and 11% of patient-visits, and 14% (pv=30) of patients by child self-report indicate suboptimal HRQOL. Even when all four symptoms were absent, 6% (pv=21) of patient-visits and 9% (pv=16) of patients by parent proxy-report, and 4.0% (pv=14) of patient-visits and 5% (pv=8) of patients by child report indicate suboptimal HRQOL.

Suboptimal HRQOL exists also for children with polyarticular JIA treated for 12 months with biologic therapies. We identified 31 polyarticular JIA patients in the database who had been treated with biologics for at least 12 months and who had a visit with a PedsQL score within 30 days of completing 12 months of treatment. The mean (SD) PedsQL Generic Core Scale score by child self-report (n = 27) was 85.4 (16.3) and by parent proxy-report (n = 28) was 81.3 (17.0). Fully 25.9% (n=7) of child self-report scores and 35.7% (n=10) of parent proxy-report scores fell in the suboptimal range. Table 3 summarizes the clinical characteristics of these patients at the time of these visits.

Discussion

This study demonstrates substantial unexplained variance in HRQOL for children with JIA experiencing minimal clinical symptoms and for children with polyarticular JIA treated with biologics for 12 months. While better clinical scores are associated, on average, with higher HRQOL, many children with no or very mild clinical symptoms continue to experience suboptimal HRQOL. Moreover, the new class of biologics, despite providing profound improvement in joint inflammation, often fails to produce optimal HRQOL in children with polyarticular JIA – 1 out of 4 children treated with biologics for at least 12 months report

suboptimal HRQOL and this proportion increases to 1 out of every 3 patients by parent proxy-report.

It is unclear how change in clinical parameters is related to improvement in HRQOL. It is therefore imperative to understand how to maximize the effects of these new treatments on HRQOL in JIA, e.g. to achieve the largest gain in HRQOL possible. This contribution would be significant because improving HRQOL is a fundamental goal of the U.S. health care system: this knowledge will enable clinicians and researchers to maximize HRQOL gains in JIA patients by tailoring existing and initiating additional interventions and to target other modifiable factors. For example, if studies were to find that functional status rather than AJC is a more important determinant of HRQOL, clinicians could tailor clinical interventions by choosing treatment interventions that maximize improved functional status. Similarly, if studies were to find that gains in HRQOL are stronger in children who have adequate social support, clinicians could counsel patients or families during discussion of treatment options and, perhaps, refer patients to a behavioral specialist to strengthen the child's social support. Future research needs to understand both medical and non-medical drivers of between patient differences in HRQOL outcomes, thus enabling clinicians to maximize HRQOL for children with JIA and to maximize the effect of JIA treatment on HRQOL.

This study has limitations. We relied on a retrospective analysis of existing data and only had access to PedsQL™ total scores for the core and the rheumatology module. While it would be useful to examine the relationship between symptoms and subscale scores for the PedsQL™, we were unable to do this with the existing data set. Our outcome variable, HRQOL, is based on parent- and child-report and is subject to acquiescence, responder bias, adaptation coping, response shift, maturity and other bias. However, the PedsQL™ has been subjected to rigorous testing of its reliability and validity – it is unlikely that such bias is systematic. In terms of generalizability, our sample was predominantly female and white, which is similar to the epidemiology of JIA (30, 31). However, further studies with higher proportions of males and non-whites would be useful in examining generalizability. Moreover, while this retrospective analysis of a clinical database represents all patients seen in the only sub-specialty clinic and regional referral center in the region and is therefore likely to be generalizable to this catchment area, it is not known to what extent these results would be generalizable to patients in other clinics or to children with this diagnosis not treated in sub-specialty clinics.

Results of this study have important implications for clinical practice. While many patients with JIA who report no or mild clinical symptoms clearly are functioning in the optimal range of HRQOL, there is a significant percentage who are not. Although disease severity is clearly associated with HRQOL it is not a proxy for this measure. HRQOL needs to be assessed independently regardless of clinical or treatment status.

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Table 1

GEE analysis of clinical characteristics on PedsQL Generic Core and Arthritis Module scores, Type 3 effect Chi-square Values and p values

Clinical Characteristic	Parent Proxy-report		Child Self-report	
	Chi-square	***P*-value**	**Chi-square**	***P*-value**
Generic Core Scale				
Active Joint Count	26.61	<.0001	15.52	<.0001
Pain Rating	86.46	<.0001	74.65	<.0001
Physician Global Assessment	47.13	<.0001	31.81	<.0001
Child Health Assessment	58.24	<.0001	37.66	<.0001
Arthritis Module				
Active Joint Count	35.05	<.0001	28.59	<.0001
Pain Rating	107.00	<.0001	99.25	<.0001
Physician Global Assessment	75.63	<.0001	57.06	<.0001
Child Health Assessment	62.68	<.0001	44.49	<.0001

*adjusted for age, gender, race, ethnicity, age onset of disease and duration of disease.

Table 2

Number of visits and patients, mean and standard deviation for PedsQL Generic Core Total Scale, and number and percent of visits and patients below the optimal PedsQL score, stratified by clinical characteristic.

Clinical Characteristic	Parent Proxy-report					Child Self-report				
	PV, N	Mean PedsQL (PV, N)	SD (Btwn, Within)	% <78.6 (PV, N)	#<78.6 (PV, N)	PV, N	Mean PedsQL (PV, N)	SD (Btwn, Within)	% <78.6 (PV, N)	#<78.6 (PV, N)
Active Joint Count										
	1135	87.07	20.88	22.91%	260	1007	88.84	18.38	17.97%	181
0	388	85.2	7.85	26.55%	103	354	86.91	6.71	21.47%	76
	314	86.07	15.58	25.48%	80	275	88.61	14.59	19.64%	54
1	191	85.72	6.39	25.13%	48	170	87.26	6.49	20.59%	35
	224	83.01	17.78	32.59%	73	187	85.06	15.03	28.34%	53
2	152	82.28	8.84	34.87%	53	130	83.98	9.11	31.54%	41
Pain Rating (0–10)										
	948	91.49	15.47	11.08%	105	817	93.12	12.76	7.59%	62
0	310	89.57	6.67	15.48%	48	282	91.04	5.23	11.35%	32
	318	86.03	15.1	25.16%	80	277	88.1	13.39	20.22%	56
1	187	85.29	8.56	29.41%	55	166	86.95	6.83	21.69%	36
	206	82.76	15.37	33.50%	69	173	85.16	14.01	27.75%	48
2	143	81.7	7.07	34.27%	49	120	83.9	7.48	31.67%	38
Physician Global Assessment (0–10)										
	821	89.05	17.26	18.39%	151	740	90.66	15.33	12.84%	95
0	313	87.45	7.6	22.36%	70	287	89.16	6.38	14.63%	42
	484	84.93	19.09	27.69%	134	432	87.44	16.45	22.22%	96
1	249	83.33	7.76	32.13%	80	227	86.01	6.91	25.99%	59
	264	82.08	17.55	34.47%	91	215	84.24	16.77	28.84%	62
2	178	81.93	7.21	34.83%	62	147	83.59	7.15	29.93%	44
Child Health Assessment Questionnaire (0–3)										
	1195	91.49	15.18	11.97%	143	1085	92.28	14.21	9.95%	108
0	348	89.86	6.62	15.23%	53	331	89.49	5.69	16.01%	53

Clinical Characteristic	Parent Proxy-report					Child Self-report				
	PV, N	Mean PedsQL (PV, N)	SD (Btwn, Within)	% <78.6 (PV, N)	#<78.6 (PV, N)	PV, N	Mean PedsQL (PV, N)	SD (Btwn, Within)	% <78.6 (PV, N)	#<78.6 (PV, N)
>0 – <=.13	223	82.84	13.14	30.49%	68	197	86.12	12.28	21.83%	43
	158	81.96	9.64	34.81%	55	139	85.07	9.03	25.18%	35
Minimal symptoms on all four characteristics										
All characteristics 0	380	94.5	8.97	5.53%	21	349	94.81	8.41	4.01%	14
	184	93.28	5.67	8.70%	16	168	93.89	4.57	4.76%	8
All characteristics <=2 (or 0.13 on CHAQ)	511	90.34	13.92	14.48%	74	461	91.55	12.85	10.85%	50
	230	88.86	7.24	18.70%	43	213	89.91	6.2	14.08%	30

Note: N = number of patients; PV = number of patient visits; N corresponds to PV within each stratum of each clinical category, rather than a unique patient within each category. For example, a given patient may have AJC=0 at one visit, but AJC = 1 at another visit: Such a patient would contribute towards N in both AJC =0 stratum and AJC = 1 stratum.

Table 3

Clinical Characteristics for patients (n = 31) with polyarticular JIA within 30 days of 12 months of treatment with biologics.

Clinical Characteristic	Number of Patients	Percent of Patients
Active Joint Count		
0	17	54.8
1	5	16.1
2 or more	9	29.1
Patient Pain Rating		
0	11	35.5
1	7	22.6
2 or more	13	41.9
Physician Global Assessment		
0	12	38.7
1	10	32.2
2 or more	9	29.1
Child Health Assessment Questionnaire		
0	15	48.4
0.13	3	9.7
≥ 0.13	13	41.9