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Association Between Patient-Reported Outcomes and Treatment Failure in Juvenile Idiopathic Arthritis

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Objective. Children with juvenile idiopathic arthritis (JIA) frequently exhibit symptoms months before diagnosis. The aims of this study were to assess whether baseline patient-reported outcomes (PROs) are associated with changes in JIA pharmacotherapy treatment and whether symptom duration prior to JIA diagnosis is associated with disease activity scores over time.

Methods. This is a retrospective cohort study of patients with an incident diagnosis of JIA. Patient-reported symptom duration, pain, energy, disease activity, sleep, anxiety, and depression screenings, as well as provider-reported disease activity and joint count, were collected during routine clinical care. Cox proportional hazards evaluated PROs, disease activity scores, and symptom duration with initial medication failure within 9 months of diagnosis. Multivariate mixed effects linear regression evaluated the association of symptom duration with disease activity scores.

Results. There were 58 children (66% female, 35% oligoarticular JIA) in the cohort. Nearly half of patients failed initial therapy within 9 months. Unadjusted analysis showed that higher energy (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.69-0.99; $P = 0.04$) and longer symptom duration (HR: 0.96; 95% CI: 0.93-0.99; $P = 0.03$) at diagnosis were protective against medication failure. Adjusted analysis showed that symptom duration prior to diagnosis was protective against medication failure (HR: 0.95; 95% CI: 0.92-0.99; $P = 0.02$); there was no association between medication failure and pain, psychiatric symptoms, or disease activity scores. There was a positive association with longer symptom duration and higher disease activity at 30 and 60 days, but this was not sustained.

Conclusion. Higher energy levels and longer symptom duration are protective against initial JIA treatment failures. Initial treatments informed by patient-reported data could lead to more successful outcomes by changes in treatment paradigms.

INTRODUCTION

Despite juvenile idiopathic arthritis (JIA) being the most common, chronic rheumatic condition of childhood, children frequently have symptoms for months to years before presenting to a pediatric rheumatologist and receiving a diagnosis (1–3). Untreated juvenile arthritis can lead to chronic pain, muscle atrophy, joint contractures, limb-length discrepancies, and abnormal growth (4–7). It is suggested that there is a critical window of opportunity to diagnose and treat this disease, and early treatment may limit unfavorable outcomes (8,9). However, treatments are only effective 50%-60% of the time, all while patients wait months to see whether their medication regimen will be efficacious for their disease (10–12).

Prior studies suggest that patients with higher pain and higher patient-reported and provider-reported global assessment scores at diagnosis had worse long-term outcomes (13,14). JIA subtype has also been a strong predictor of who will achieve remission (14). Clinical prediction models suggest that a tender joint count can predict who will respond to etanercept therapy (15), but additional models have not been developed to evaluate which patients will respond to initial therapy or will require future changes to their medication regimen. Fatigue is reported in more than two thirds of children with JIA, and it has been associated with disease activity, pain, psychosocial factors, and sleep (16). Despite this knowledge about long-term outcomes, it remains unclear which patients will respond favorably to a specific initial therapy based upon initial patient and disease characteristics.

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Similarly, although the components of the juvenile arthritis disease activity score can identify patient subgroups, such as patients with high baseline patient global score or elevated joint counts, these subgroups do not predict disease course nor response to therapy (17). In addition, evaluation of patient-reported outcomes (PROs) provides additional information about physical function, pain, and quality of life (18) and can be collected during a clinic visit to provide patient-centered care. Recent published data report that patient-reported assessments provide important insight on disease status and can be used to inform clinical care (19,20). Leveraging PROs could add additional information to predict treatment success, although how to routinely use these measures to inform care is not yet established (21).

The aims of this study were to assess 1) whether baseline patient- and provider-reported outcomes are associated with treatment failure in patients with an incident JIA diagnosis and 2) whether symptom duration prior to JIA diagnosis is associated with disease activity over time.

PATIENTS AND METHODS

Setting. This is a retrospective cohort study conducted at Wake Forest Baptist Health in North Carolina between 2015 and 2019. This study was approved by the Wake Forest University Health Sciences Institutional Review Board (IRB00059444).

Study population. Children who were seen at a tertiary academic medical center outpatient pediatric rheumatology clinic with an incident diagnosis of JIA were included. Manual chart review confirmed JIA diagnosis, JIA subtype (22), date of diagnosis, and duration of symptoms prior to diagnosis. Analysis was limited to 9 months after diagnosis.

Measurement of PROs. As part of routine outpatient clinical care, the clinic electronically captures PROs in either English or Spanish based upon the patient's primary language, and results are integrated into our electronic health record (EHR). Questionnaires are administered to the patient or caregiver prior to the provider visit. Pain and energy were assessed with the following questions, respectively: "On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain, how much pain do you have today?" and "On a scale of 0 to 10, with 0 being no energy and 10 being the most energy, how much energy do you have today?", with 0-10 ordinal response options. Patient disease activity was assessed with the question "How do you rate your disease activity over the past week?" with 0-10 ordinal response options; higher rating indicates higher disease activity. Psychiatric symptoms were screened with the questions "Do you have difficulties falling or staying asleep?", "Do you feel sad, blue, down, or depressed?", and "Do you feel nervous or anxious?" with dichotomous response options.

Measurement of provider-reported outcomes. As part of routine outpatient clinical care, providers discretely enter joints that are swollen, tender, and/or have decreased range of motion into the EHR at all visits. Active joint count is defined as the total number of swollen joints. A joint with both decreased motion and tenderness was considered swollen. Provider global disease activity score was entered on a 0-10 ordinal response scale; a higher rating indicates higher disease activity. For patients who were hospitalized at diagnosis, baseline active joint count was obtained through manual chart review.

Disease activity score. The Clinical Juvenile Arthritis Disease Activity Score-10 (23) (cJADAS-10) was calculated as a composite score of the sum of patient global disease activity score (using a 0-10 scale), provider global disease activity score (using a 0-10 scale), and active joint count (with a maximum of 10 joints) for all available clinic visits. The cJADAS-10 score ranges from 0 to 30, with a higher score indicating more active disease.

Baseline medication exposure. Initial treatment is defined as the systemic pharmacotherapy prescribed or receipt of intraarticular corticosteroid injection within the first 21 days of diagnosis. Treatment regimens were determined through shared decision-making between the patient and provider.

Outcomes. Treatment failure is defined as the visit date when additional treatment was prescribed. Medication dose or route changes were not considered treatment failures. Reason for treatment failure was recorded. Medication data were validated through manual chart review.

Missing data. Multiple imputation by chained equations (24,25) was used to estimate missing data. For the continuous variables of pain, energy, patient global score, provider global score, and cJADAS-10, linear regression was used to estimate missing baseline scores. For the binary variables of sleep difficulties, depression, and anxiety, logistic regression was used to estimate baseline responses. Age, sex, ethnicity, race, antinuclear antibody serology, and symptom duration informed each imputation. Data were missing at random except for those who were diagnosed inpatient. Patient and provider global assessment capture were integrated into routine clinical care midway through the study period.

Analysis. Baseline demographics and clinical characteristics were summarized as count (%) or median and interquartile range (IQR); differences were tested for significance with the X^2 test or Wilcoxon rank-sum test of equality, as appropriate. Kaplan-Meyer curves show PROs stratified into low and high exposures based upon the median reported value at the time of diagnosis. Low energy was defined as initial energy of less than

7. High pain was defined by the initial median score of more than 3.3. High disease activity score was defined as initial cJADAS-10 of more than 8.5 (26). Prolonged symptom duration was defined as 6 months or more. Unadjusted univariate Cox proportional hazards were used to model the association between time to treatment failure and each PRO, provider disease assessment, cJADAS-10 score, and symptom duration (in months), and include active joint count as a time-varying covariate. Multivariate Cox models include adjustment for initial treatment with disease modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, intraarticular corticosteroid injections, and oligoarticular JIA subtype; active joint count was a time-varying covariate. Patients with only one visit were included within Cox models as they provided baseline data. Sensitivity analysis was limited to subjects with nonsystemic JIA.

We used multivariate mixed effects linear regression modeling with random intercepts to evaluate the association of symptom duration more than 6 months before diagnosis and the cJADAS-10 score over time. Fixed effects included initial prescribed DMARD, NSAID, systemic corticosteroids, intraarticular corticosteroid injections, and oligoarticular JIA subtype, and a symptom duration by diagnosis duration interaction. The interaction allowed us to measure the difference between disease activity score and symptom duration prior to JIA diagnosis at each time point. Subject was treated as a random effect to account for repeated measures within each patient. Analysis was completed using Stata 16.0.

RESULTS

There were 58 patients with an incident diagnosis of JIA during the study period. Thirty-eight (66%) were female, and 20 (34%) had oligoarticular JIA (Table 1). Eight patients did not have a follow-up visit. At diagnosis, the raw median patient-reported pain, energy, and global disease activity scores were 3 (IQR 0-6), 7 (5–9), and 6 (4–7), respectively. Baseline pain, energy, sleep, anxiety, and depression were complete in 47/58 patients. Patient global and provider global scores were complete in 25/58 subjects (see Supplementary Table 1 for imputed assessments.) More than one quarter of patients reported sleep difficulty or anxiety, and 13% reported feeling depressed. The median symptom duration before JIA diagnosis was 9.2 months (IQR 4.9-30.4); median symptom duration for systemic JIA was 29 days (IQR 15-31). Demographics and baseline PROs did not differ among those who did or did not require changes in treatment within the first 9 months after JIA diagnosis. DMARDs and intraarticular corticosteroid injections were the most frequent initial therapies. No patients initially started both biologic and nonbiologic DMARDs.

There were 18.7 total person-years of follow-up included in the analysis. The median time in the cohort was 102 days (IQR 45-200). Twenty-eight (48%) patients failed their initial therapy within the first 9 months. Median time to medication failure was 98 days (IQR 54-186). Clinical characteristics of those who failed initial therapy are as follows: there were 19 (66%) female patients and 22 (79%) White patients, and failure was most common among subjects with oligoarticular and rheumatoid-factor negative polyarticular JIA (N = 8 [28%] and N = 7 [25%], respectively). Among those who required change in therapy, 2 (7%) developed new-onset uveitis, 23 (82%) had active arthritis, and 5 (18%) had medication side effects; 2 patients failed therapy for multiple reasons.

Univariate evaluation of baseline PROs showed that higher baseline energy was protective against medication failure (hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.69-0.99; $P = 0.04$; Table 2, Figure 1A). There was no association between baseline pain, psychiatric symptoms, patient or provider global score, or disease activity score among those who did and did not fail therapy within the first 9 months (Figure 1B-C). Longer symptom duration in months was protective against medication failure (HR: 0.96; 95% CI: 0.93-0.99; $P = 0.03$; Figure 1D). After adjusting for baseline medication exposure and oligoarticular JIA, symptom duration was protective against therapy failure (HR: 0.95; 95% CI: 0.92-0.99; $P = 0.02$). When limiting to subjects without systemic JIA, only symptom duration remained significant in multivariate analysis (Supplementary Tables 2 and 3). There was a positive association with longer symptom duration and disease activity at 30 and 60 days, but this association was not sustained thereafter (Table 3).

DISCUSSION

In this study of 58 children with an incident JIA diagnosis at a single tertiary pediatric rheumatology clinic, we found that higher baseline energy and longer symptom duration prior to diagnosis were protective against initial pharmacotherapy failure in univariate analysis. After accounting for initial pharmacotherapy and oligoarticular JIA subtype, as well as the active joint count across all visits, symptom duration prior to diagnosis had lower hazards of failing initial therapy. However, there was no association of treatment failure with baseline patient-reported pain, sleeping concerns, anxiety, or depression. Similarly, there was no association with initial patient- or provider-reported disease activity nor with the juvenile arthritis disease activity score and treatment failure. When evaluating across all visits, we found that longer symptom duration prior to diagnosis was initially associated with higher disease activity scores, but this was not sustained over time. This study adds that the evaluation of baseline patient and clinical characteristics could be used in clinical decision-making to guide initial pharmacotherapy choices, which could lead to more successful outcomes and changes in treatment paradigms.

Multiple factors contribute to a patient's perceived level of energy, including physical activity, sleep disturbances, age, and

Table 1. Baseline demographics

	All patients (N = 58)	No failure within 9 mon (n = 30)	Failure within 9 mon (n = 28)	P value
Age in y, median [IQR]	10.8 [6.5-14.9]	11.3 [8.2-15.6]	10.7 [4.1-14.6]	0.24
Joint count at diagnosis, median [IQR]	2 [1-5]	2 [1-3]	3 [1.5-5]	0.08
Symptom duration in mon, median [IQR]	9.2 [4.9-30.4]	13.9 [4.9-30.4]	5.9 [3.5-26.4]	0.18
Female sex	38 (66%)	19 (63%)	19 (68%)	0.72
Hispanic ethnicity	9 (16%)	4 (13%)	5 (18%)	0.63
Race				0.40
Black	7 (12%)	5 (17%)	2 (7%)	
White	41 (71%)	19 (63%)	22 (78%)	
Other	10 (17%)	6 (20%)	4 (15%)	
JIA subtype				0.17
Oligoarticular	20 (34%)	12 (40%)	8 (29%)	
RF+ polyarticular	4 (7%)	3 (10%)	1 (3%)	
RF− polyarticular	11 (19%)	4 (13%)	7 (25%)	
Systemic	7 (12%)	2 (7%)	5 (18%)	
Psoriatic	3 (5%)	0 (0%)	3 (11%)	
Enthesitis-related	8 (14%)	6 (20%)	2 (7%)	
Undifferentiated	5 (9%)	3 (10%)	2 (7%)	
Incident visit PROs[a]				
Pain, median [IQR]	3 [0-6]	3 [0-7]	3 [0-6]	0.89
Energy, median [IQR]	7 [5-9]	7 [6-9]	5 [5-8]	0.25
Patient global score, median [IQR]	6 [4-7]	7 [1-7]	5 [4-7]	0.72
Sleeping difficulty	11 (23%)	5 (20%)	6 (27%)	0.56
Anxiety	13 (28%)	6 (24%)	7 (32%)	0.55
Depression	6 (13%)	4 (16%)	2 (9%)	0.48
Provider global score, median [IQR]	4 [3-6]	4 [2.5-6]	4 [3-7]	0.44
cJADAS-10, median [IQR]	12 [10-17]	11.5 [9-15]	13 [11-17]	0.22
Initial therapy[b]				0.30
DMARD	37 (64%)	16 (53%)	21 (75%)	
Nonbiologic	25 (43%)	10 (33%)	15 (54%)	
Biologic	12 (21%)	6 (20%)	6 (21%)	
NSAID	9 (16%)	5 (17%)	4 (14%)	
Systemic corticosteroid	4 (7%)	1 (3%)	3 (11%)	
Intraarticular corticosteroid	13 (22%)	9 (30%)	4 (14%)	

Abbreviations: cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score-10; DMARD, disease modifying antirheumatic drug; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PRO, patient-reported outcome; RF, rheumatoid factor.
[a]Reported values are for non-missing data. Baseline pain, energy, sleep, anxiety, and depression were complete in 47/58 patients. Patient global and provider global scores were complete in 25/58 subjects.
[b]Patient could start multiple initial therapies.

Table 2. Hazard ratios of baseline patient- and provider-reported outcomes and initial medication failure

	Unadjusted		Adjusted	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Pain	1.07 (0.90-1.28)	0.42	1.12 (0.92-1.35)	0.26
Energy	0.82 (0.69-0.99)	0.04	0.82 (0.64-1.02)	0.08
Sleeping difficulty	1.95 (0.71-5.38)	0.19	2.24 (0.76-6.61)	0.15
Anxiety	1.77 (0.66-4.76)	0.26	1.81 (0.61-5.36)	0.25
Depression	0.57 (0.10-3.42)	0.54	0.60 (0.09-3.84)	0.59
Patient global score	1.02 (0.91-1.15)	0.67	1.01 (0.89-1.19)	0.72
Symptom duration	0.96 (0.93-0.99)	0.03	0.95 (0.92-0.99)	0.02
Provider global score	1.05 (0.96-1.16)	0.26	1.00 (0.94-1.07)	0.88
cJADAS-10	1.00 (0.99-1.01)	0.72	1.00 (0.98-1.01)	0.93

Note: Active joint count was included as a time-varying covariate in all models. Multivariate models were adjusted for initial medication exposure (disease modifying antirheumatic drugs, intraarticular corticosteroid injection, nonsteroidal anti-inflammatory drugs, systemic steroids), and oligoarticular juvenile idiopathic arthritis subtype.
Abbreviation: cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score-10.
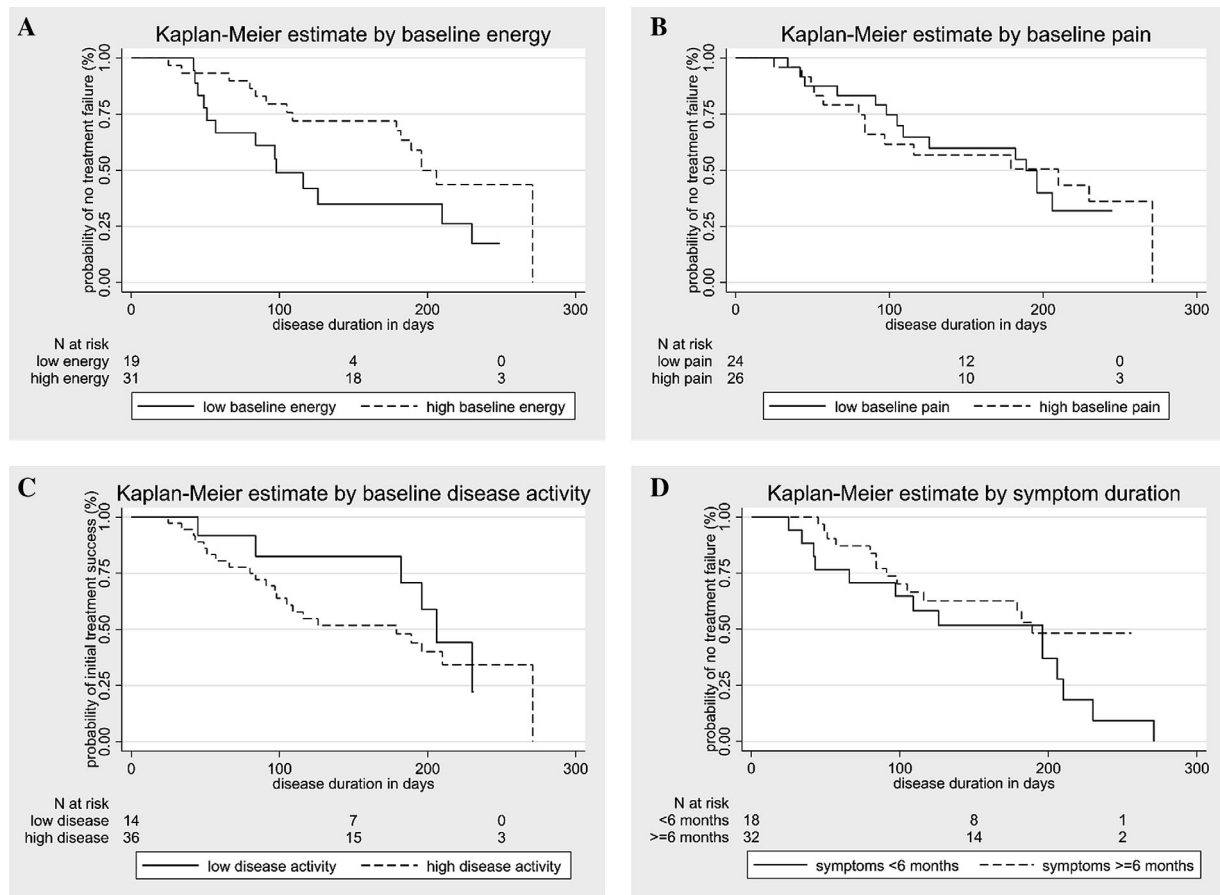
Figure 1. Kaplan-Meier survival estimates stratified by baseline patient-reported energy, pain, disease activity, and symptom duration. **(A)** Low and high energy levels are defined as less than 7 and as greater than or equal to 7, respectively. **(B)** Low and high pain levels are defined as less than 3 and as greater than or equal to 3, respectively. **(C)** Low and high disease activity scores are defined as initial cJADAS-10 scores of greater than or equal to 8.5 and as less than 8.5, respectively. **(D)** Symptom duration was stratified at 6 months. cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score-10.

behavior (27,28). Low energy has been associated with both lower levels of physical activity and higher physical disability (29). It is possible that children with low energy are unable to successfully complete daily activities or participate in extracurricular activities because of their disease. It is also possible that decreased physical activity promotes muscle atrophy and stiffness, which can intensify

Table 3. Differences in cJADAS-10 scores in patients with symptom duration of less than or greater than 6 months

Time since JIA diagnosis	β coefficient (95% CI)	P value
30 d	12.31 (3.89 to 20.75)	<0.01
60 d	9.50 (1.18 to 17.81)	0.03
90 d	6.67 (−2.80 to 16.15)	0.17
120 d	3.85 (−7.68 to 15.39)	0.51
180 d	−1.79 (−18.72 to 15.15)	0.84

Note: Models were adjusted for initial medication exposure (disease modifying antirheumatic drug, intraarticular corticosteroid injection, nonsteroidal anti-inflammatory drug, systemic corticosteroids) and oligoarticular juvenile idiopathic arthritis subtype.
Abbreviations: cJADAS-10, Clinical Juvenile Arthritis Disease Activity Score-10; JIA, juvenile idiopathic arthritis.

abnormal biomechanics which are present in youth with JIA (30–33). Similarly, both JIA alone, as well as imposed or perceived physical activity limitations, may contribute to this finding.

Shorter symptom duration prior to diagnosis may indicate more severe disease or more prominent features that could lead to an expedited diagnosis of JIA; those with systemic JIA, which presents with noticeable fevers and rashes, had a shorter time to diagnosis than other subtypes, which is in accordance with other studies (2). However, when excluding subjects with systemic JIA, results were similar. Oligoarticular and rheumatoid-factor negative polyarticular JIA subtypes failed therapy; this may suggest that current treatment approaches are insufficient to establish and/or maintain disease control.

This also highlights that incorporating PROs into routine clinical care aids in understanding disease and treatment outcomes. Patients offer unique perspectives on their disease, and often provider and patient assessments differ (34). Leveraging PROs to guide initial treatment plans could lead to more individualized and personalized care and may suggest the need for changes in

treatment paradigms. For example, if a patient reports lower energy upon diagnosis, it is possible that current first-line treatment options will not adequately control the patient's disease, and more aggressive or alternative initial therapies should be recommended. Although the JADAS score, which contains patient and provider global scores, is considered in treatment guidelines, other PROs are not currently components of JIA treatment recommendations (35–37).

There was an early, but not sustained, association between prolonged symptom duration and disease activity score over time. Prior studies show that only 50%-60% of patients reach Pediatric American College of Rheumatology (ACR) 50% criteria at 3 months, and only approximately 25% of patients reach Pediatric ACR 90% (38). Although we did not evaluate the ACR Pediatric 30/50/70/90 criteria, the cJADAS-10 components are embedded within ACR scoring. Similarly, although our findings are likely due to censoring as patients who changed therapies were excluded from analysis upon initial treatment failure, it does highlight that there may be a critical window of opportunity to adequately treat and control disease (8).

This study has multiple strengths. First, we collect PROs on all patients as part of regular clinical practice; response bias is lessoned as patients complete questionnaires before being evaluated by a provider or receiving a diagnosis. Second, our study includes real-world data. All children evaluated by the clinic were included, whereas other literature is limited to only when a child is enrolled within a study. Third, we leveraged our EHR to collect interesting data elements as standard-of-care, highlighting the importance of data collected for clinical care, which can also be used for research. Fourth, we collect PROs in multiple languages that were officially translated by a certified interpreter; this decreases communication barriers and results in a more inclusive study cohort.

This study must be interpreted in light of several limitations. First, we had missing baseline data; however, we leveraged multiple imputation to make informed estimates. Most missing data were missing at random, in part because of adding additional PROs to our questionnaires over the course of the study period. Five patients hospitalized at diagnosis did not complete baseline PROs, and it is possible that these imputed values were less reflective of their true values given the hospitalization. Second, many of our PRO questions, such as psychiatric screening questions, are not validated. However, the wording of these PROs align with questions asked during review of systems. We were unable to implement electronic screenings of validated depression or anxiety questionnaires given limitations imposed by the hospital's information technology security and compliance teams. Nonetheless, our positive screening rates are similar to those reported among children with chronic conditions (39). Lastly, the choice and duration of initial therapy may be guided by insurance protocols; we attempted to decrease confounding by including baseline therapies and active joint counts across visits in our analysis. Likewise, we limited analysis to 9 months because most insurance protocols would consider this a sufficient trial of therapy.

In conclusion, energy levels and symptom duration were associated with initial JIA treatment outcomes. Treatments informed by patient-reported data could possibly promote more effective disease control and result in changes in treatment paradigms.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Taxter 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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Acquisition of data. Taxter, Donaldson, Harry.
Analysis and interpretation of data. Taxter.

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