

The Juvenile Psoriatic Arthritis Cohort in the CARRA Registry: Clinical Characteristics, Classification, and Outcomes

Devy Zisman, Dafna D. Gladman, Matthew L. Stoll, Vibeke Strand, Idit Lavi, Joyce J. Hsu, Elizabeth D. Mellins, and the CARRA Legacy Registry Investigators

ABSTRACT. Objective. Children with clinically diagnosed juvenile psoriatic arthritis (JPsA) who were enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry (CARRA-JPsA) were classified according to pediatric International League of Associations for Rheumatology (ILAR) and adult criteria [Classification criteria for Psoriatic Arthritis (CASPAR)]. Data on demographic and clinical features at baseline and 1-year followup were analyzed and compared.

Methods. Cross-sectional analysis was performed of CARRA-JPsA patients enrolled between May 2010 and December 2013 and stratified according to age at disease onset (\leq or $>$ 4 yrs). Features of patients fulfilling ILAR and CASPAR criteria were compared at baseline and followup using chi square, Fisher's exact, Mann-Whitney-McNemar, Wilcoxon signed rank, and t tests, as appropriate.

Results. Among 361 children enrolled as CARRA-JPsA, 72.02% had symptom onset at $>$ 4 years of age, with a male predominance and high prevalence of enthesitis. At followup, statistically significant improvements were reported in arthritis, dactylitis, enthesitis, psoriasis, sacroiliitis, and nail pitting, but not in health questionnaire (HQ) scores. Of the patients, 80.5% fulfilled ILAR criteria for JPsA. Fifty-two patients, whose disease fulfilled CASPAR criteria but had not been included in the JPsA cohort, manifested more enthesitis, sacroiliitis, inflammatory bowel disease and uveitis and less psoriasis.

Conclusion. The data support division of patients with JPsA into 2 clinical subgroups, according to age at disease onset. Improvement in objective findings did not correlate with changes in HQ scores. Pediatric rheumatologists currently do not diagnose JPsA in all children whose disease manifestations meet CASPAR criteria. Unification of adult and pediatric PsA classification criteria warrants consideration. (J Rheumatol First Release February 1 2017; doi:10.3899/jrheum.160717)

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Children with juvenile psoriatic arthritis (JPsA) are a heterogeneous group of pediatric patients who can present with features similar to other juvenile idiopathic arthritis (JIA) subtypes. The literature is sparse and inconsistent regarding

features of JPsA. Hamilton, *et al*, comparing 28 patients with JPsA to 158 patients with adult PsA, described a similar clinical picture in both groups, with progression from oligoarthritis to polyarthritis and a favorable outcome¹.

From the Department of Rheumatology, and the Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel; The Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; Psoriatic Arthritis Program, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital, Toronto, Ontario, Canada; Department of Pediatrics, Division of Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama; Department of Medicine, and Department of Pediatrics, Division of Immunology and Rheumatology, Stanford University, Palo Alto, California; Department of Pediatrics, Divisions of Human Gene Therapy and Allergy, Immunology and Rheumatology, Program in Immunology, Stanford University, Palo Alto, California, USA.

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D. Zisman, MD, Department of Rheumatology, Carmel Medical Center,

and the Ruth and Bruce Rappaport Faculty of Medicine, Technion; D.D. Gladman, MD, FRCPC, Psoriatic Arthritis Program, Centre for Prognosis Studies in The Rheumatic Diseases, Toronto Western Hospital; M.L. Stoll, MD, PhD, MSCS, Department of Pediatrics, Division of Rheumatology, University of Alabama at Birmingham; V. Strand, MD, FACP, FACR, Department of Medicine, Division of Immunology and Rheumatology, Stanford University; I. Lavi, MA, Department of Community Medicine and Epidemiology, Carmel Medical Center; J.J. Hsu, MD, Department of Pediatrics, Division of Allergy, Immunology and Rheumatology, Stanford University; E.D. Mellins, MD, Department of Pediatrics, Divisions of Human Gene Therapy and Allergy, Immunology and Rheumatology, Program in Immunology, Stanford University.

Dr. Gladman, Dr. Stoll, and Dr. Strand contributed equally to this paper and are listed alphabetically.

Address correspondence to Dr. D. Zisman, Department of Rheumatology, Carmel Medical Center, 7 Michal St., Haifa 34362, Israel.

E-mail: devyzisman@gmail.com

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Butbul Aviel, *et al*, analyzing data from 122 children with JPsA, reported no significant differences with JIA patients in presentation, disease course, associated uveitis, response to treatment, and outcome². In contrast, Flato, *et al* reported that patients with JPsA have genetic markers different from other JIA subtypes and more progressive, persistent disease³. Studies demonstrate more encouraging responses with ~60% of patients achieving remission after a median followup of 23 months⁴. Two different classification systems of JPsA have been proposed: first the Vancouver criteria⁵, followed by the International League of Associations for Rheumatology (ILAR) classification, published in 2004⁶.

Applying ILAR criteria to classify subjects as having JPsA, many children with axial involvement are likely to be classified as enthesitis-related arthritis (ERA) or undifferentiated JIA⁶. In contrast, Classification criteria for Psoriatic Arthritis (CASPAR), developed for adults, incorporate musculoskeletal manifestations including axial and peripheral arthritis, enthesitis, and cutaneous and radiographic features; based on a prospective study of patients with PsA compared to patients with other forms of inflammatory arthritis⁷.

Here, we performed descriptive analyses of the disease manifestations at enrollment and after 1 year of children in the original Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry (called “the legacy registry”) and coded by their physician as JPsA (“the CARRA-JPsA cohort”). We investigated differences between this CARRA-JPsA cohort and patients who fulfilled ILAR (ILAR-JPsA) versus CASPAR (CASPAR-JPsA) classification criteria, respectively.

MATERIALS AND METHODS

We conducted a retrospective study using the CARRA legacy registry of children with pediatric rheumatic diseases. The CARRA legacy registry is a convenience registry, in which disease-specific cohorts were defined by treating physician diagnosis, and patients at any stage of disease were eligible for enrollment. It has been used in other published reports^{8,9,10}. Between May 2010 and December 2013, the registry enrolled 9450 patients from > 100 sites in the United States and Canada.

Patients diagnosed by their treating rheumatologist with JPsA were studied at enrollment and at the 1-year followup. The following variables, as reported by the treating physician, were analyzed: demographics, including age at first symptom, age at diagnosis, sex, race, ethnicity, first-degree family history of psoriasis, arthritis, and inflammatory bowel disease (IBD); clinical measures, including arthritis (oligoarthritis, < 5 joints involved; polyarthritis, ≥ 5), enthesitis, dactylitis and nail pitting, sacroiliitis/inflammatory back pain (IBP), past or current psoriasis, uveitis, and IBD; and laboratory variables, including rheumatoid factor (RF), anti-nuclear antibodies (ANA), anticyclic citrullinated peptide antibodies (ACPA), and HLA-B27 status. Radiographic data, including joint space narrowing, erosion or ankylosis, and computed tomography or magnetic resonance imaging evidence of damage or active inflammation involving the sacroiliac joint were reported as evidence of peripheral joint damage. Treatment data included present or past use of nonsteroidal antiinflammatory drugs (NSAID), glucocorticoids (GC) by route of administration (intra-articular injection, intravenous pulses, or orally), disease-modifying antirheumatic drugs [DMARD; azathioprine, cyclosporine, hydroxychloro-

quine, leflunomide, methotrexate (MTX), or sulfasalazine], and biologic DMARD (bDMARD), e.g., tumor necrosis factor (TNF) inhibitors. The health questionnaires (HQ) collected in the database included parent/subject overall well-being (GLASWBSC), measured on a 10-cm visual analog scale (VAS); parent/subject pain scale (PAINSC), measured on a 10-cm VAS; health-related quality of life (HRQOL), scored by parent/patient as 1 = excellent to 5 = very poor; Childhood Health Assessment Questionnaire (CHAQ), scored as 0 = best and 3 = worst; physician assessments of American College of Rheumatology (ACR) functional status (Class I to Class IV) and global disease activity (PHYGLBSC), measured on a 10-cm VAS. JPsA subgroups were compared and divided according to age of symptom onset, as defined by Lilliefors-corrected Kolmogorov-Smirnoff test applied to an age-of-onset histogram (≤ 4 and > 4 yrs). Outcomes after 1 year of followup were assessed by objective and subjective findings. Objective findings (Model 1) were defined as the change in the prevalence of patients having arthritis, dactylitis, enthesitis, psoriasis, sacroiliitis, and nail pitting. Subjective findings (Model 2) were defined as the change in the numeric score of HQ: PAINSC, HRQOL, CHAQ, GLASWBSC, and PHYGLBSC. We assessed the influence of demographic variables on outcomes at followup: age at onset (≤ 4 and > 4 yrs), ethnicity (Hispanic vs non-Hispanic), race (white vs nonwhite), sex, and treatment regimen (daily NSAID, GC ever, DMARD, bDMARD).

We developed algorithms to classify patients as ILAR-JPsA or CASPAR-JPsA (Supplementary Table 1, available with the online version of the article); these algorithms were modified from the published ILAR and CASPAR criteria, owing to absence of certain information in the CARRA database^{6,7}. The ILAR algorithm consisted of arthritis and psoriasis or arthritis and 2 of the following: dactylitis, nail pitting, and family history of psoriasis. We excluded patients who fulfilled 1 of the following criteria: arthritis in a HLA-B27+ male starting after age 6, ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, reactive arthritis, uveitis (because of a lack of information in the registry distinguishing acute and chronic uveitis), or a family history of those diseases; presence of RF positivity twice, and presence of systemic JIA⁶. The CASPAR algorithm included arthritis or enthesitis or IBP (equivalent in our cohort to sacroiliitis) and 3 additional criteria from the following: family history of psoriasis, nail involvement (equivalent to nail pitting in our database), RF-negative, history of psoriasis, current or past dactylitis (equivalent each to 1 point), and current psoriasis (equivalent to 2 points). Radiographic information in the database was insufficient for use in the CASPAR algorithm⁷. The 2 algorithms were applied to the CARRA-JPsA cohort and to the entire CARRA registry JIA cohort to compare data between those who fulfilled ILAR or CASPAR criteria and those who did not.

Statistical methods. Comparisons of categorical characteristics for the entire study group and within each subgroup were performed using chi-squares or Fisher’s exact test for small sample sizes. To compare continuous variables between 2 independent groups, t tests or the Mann-Whitney U test were used, as appropriate. Kruskal-Wallis test was used for comparisons of 3 independent groups. Comparison of dichotomous variables between enrollment and followup visits was performed using the McNemar test, whereas for continuous variables, paired t test or Wilcoxon-related test was used. Logistic regression models were used to assess the influence of treatment (DMARD, bDMARD, NSAID, steroids) on objective outcomes, defined as improvement in at least 5 variables (dactylitis, psoriasis, enthesitis, nail pitting, IBP, arthritis), controlling for age, sex, race, and ethnicity in Model 1. The influence of treatment on HQ scores, defined as improvement in all variables (PAINSC, HRQOL, CHAQ, GLASWBSC and PHYGLBSC), controlling for age, sex, race, ethnicity, and disease manifestations at enrollment, was assessed in Model 2. This model was found to be the best for discriminating between the subjective outcomes at followup compared to baseline. OR and 95% CI were calculated. Statistical significance was defined as $p \leq 0.05$. Hochberg and Benjamini correction for multiple tests was conducted¹¹. Statistical analyses were performed using IBM SPSS version 22.0 (SPSS Inc.). The study was approved by human subjects’ review

Table 1. Comparison between CARRA-JPsA onset before or at age 4 years (early onset*) and after 4 years (late onset**).

Variable	Total CARRA-JPsA, 361 Patients	Early Onset, 82 Patients	Late Onset, 260 Patients	p***
Demographic data				
Age at first rheumatology visit, yrs, mean \pm SD	9.37 \pm 4.54	3.12 \pm 2.08	11.25 \pm 3.19	
Time between symptom onset and first rheumatology visit, mean \pm SD	1.04 \pm 1.46	1.24 \pm 1.80	0.97 \pm 1.34	NS
Sex, male, n (%)	137 (38)	18 (22.0)	110 (42.3)	0.001
Family history of psoriasis, n (%)	113 (31.3)	26 (31.9)	83 (31.9)	NS
Clinical characteristics, n/total (%)				
Oligoarthritis	160/358 (44.7)	37/82 (45.1)	115/257 (44.7)	NS
Polyarthritis	198/358 (55.3)	45/82 (54.9)	142/257 (55.3)	NS
Nail pitting	128/341 (37.5)	23/77 (29.9)	93/245 (38.0)	NS
Dactylitis	102/344 (29.7)	32/78 (41.0)	65/247 (26.3)	0.013
Psoriasis	233/349 (66.8)	45/78 (57.7)	179/253 (70.8)	0.031
Enthesitis	112/342 (32.7)	13/77 (16.9)	91/247 (36.8)	0.001
Sacroiliitis	57/342 (16.7)	6/77 (7.8)	47/247 (19.0)	0.02
Uveitis	39/348 (11.2)	15/80 (18.8)	22/249 (8.8)	0.015
Questionnaires, mean \pm SD				
HRQOL score	2.17 \pm 0.84	2.02 \pm 0.89	2.21 \pm 0.84	NS
Parent/subject overall well-being score	2.33 \pm 2.20	1.83 \pm 1.80	2.54 \pm 2.31	0.03
Parent/subject pain scale score	2.58 \pm 2.64	2.12 \pm 2.53	2.75 \pm 2.69	0.05
PGA	1.50 \pm 1.71	1.41 \pm 1.78	1.53 \pm 1.72	NS
Radiographic characteristics				
Imaging evidence of joint damage, n/total (%)	74/301 (24.6)	17/67 (25.4)	50/216 (23.1)	NS
Laboratory data, n/total (%)				
ACPA	7/136 (1.9)	0/35 (0)	7/94 (7.4)	NS
RF	17/361 (4.7)	3/82 (3.7)	13/260 (5.0)	NS
ANA	135/292 (46.2)	42/68 (61.8)	87/210 (41.4)	0.003
HLA-B27	26/246 (10.6)	5/49 (10.2)	18/182 (9.9)	NS
Medications, n/total (%)				
DMARD ever	294/361 (81.4)	71/82 (86.6)	206/258 (79.8)	NS
bDMARD ever	191/361 (52.9)	49/82 (59.8)	127/258 (49.2)	NS
GC	188/361 (52.1)	53/82 (64.6)	122/260 (46.9)	0.005
Intraarticular GC	118/361 (32.7)	38/82 (46.3)	70/260 (26.9)	0.001
Daily NSAID	160/361 (44.3)	25/78 (32.1)	131/256 (51.2)	0.003
MTX	181/361 (50.14)	39/82 (47.6)	142/260 (54.6)	NS

* Early onset \leq 4 years from the total of 342 patients with known age of disease onset. ** Late onset $>$ 4 years from the total of 342 patients with known age of disease onset. *** Specific values for $p \leq 0.05$ are reported. After adjustment for multiple comparisons, the significance cutoff is $p \leq 0.006$. CARRA: Childhood Arthritis and Rheumatology Research Alliance; JPsA: juvenile psoriatic arthritis; HRQOL: health-related quality of life; PGA: physician's global assessment; ACPA: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; ANA: antinuclear antibody test; DMARD: disease-modifying antirheumatic drug; GC: glucocorticosteroids; NSAID: nonsteroidal antiinflammatory drugs; MTX: methotrexate; NS: nonsignificant.

at Stanford University and by the CARRAnet Data/Sample Share Committee (IRB-31221).

RESULTS

CARRA-JPsA cohort. The CARRA-JPsA cohort included 361 children, representing 5.6% of the total JIA cohort in the CARRA legacy registry. Their characteristics are shown in Table 1. Average age at symptom onset was 8.34 ± 4.57 years, with a delay of 1.04 ± 1.46 years from first symptom until first pediatric rheumatology appointment. The majority was white (93.9%), non-Hispanic (91.7%), and with a female predominance (62%). Musculoskeletal manifestations included polyarthritis (55.3%), oligoarthritis (44.7%), enthesitis (32.7%), dactylitis (29.7%), and sacroiliitis/IBP (16.7%). Extraarticular involvement included psoriasis

(66.8%), nail pitting (37.5%), uveitis (11.2%), and IBD (1.4%). Family history of related diseases included 31.3% with psoriasis, 1.4% with spondyloarthritis (SpA), and 1.7% with IBD. Laboratory data revealed positive ANA in 46.2%; RF in 4.7%; and HLA-B27 in 10.6%. Radiographic evidence of joint damage and sacroiliitis at enrollment was noted in 24.6% of 301 and 8 of 37 patients with imaging data reported, respectively.

At enrollment, 44.3% of patients with CARRA-JPsA were receiving NSAID, and 52.1% had ever been treated with GC. DMARD were prescribed to 81.4%, the most common being MTX (50.1%). The percentage of patients treated with bDMARD (particularly TNF inhibitors) was 52.9%. The most common bDMARD was etanercept (40.7%). The vast majority (81.3%) was assessed as functional ACR class 1.

Followup data at 1 year. One-year followup data were available for 222 patients (61.5%). At this time, statistically significant improvements were reported in all objective clinical outcomes (Table 2).

Fewer children had polyarthritis (10.3% vs 61.8%, $p < 0.0001$), 59 (46.8%) improved from polyarthritis to oligoarthritis, arthritis resolved in 50 (39.7%) from polyarthritis and 48 (61.5%) from oligoarthritis groups, 4 (5.1%) worsened from oligoarthritis to polyarthritis, and in the rest no change was found in joint count category. Improvements were noted in the frequency of nail pitting, dactylitis, psoriasis, enthesitis, clinical sacroiliitis, and uveitis. No radiographic worsening was recorded. Improvements in objective outcomes were not accompanied by improvements in HQ scores (Table 2). Assessing the influence of demographics and treatment regimen on objective outcomes, we found that children with a younger age at disease onset and females had a better outcome, by univariate and multivariable analysis (Model 1; Table 3). Patients with enthesitis had a better HQ score outcome in univariate ($p = 0.016$) and multivariable models (OR 4.14, 95% CI 1.12–15.25; Model 2, Table 3). This same trend was noted in patients with nail pitting, although it did not reach statistical significance.

Subgroups defined by age of symptom onset. The age of symptom onset was reported in 342 children. Consistent with previous studies, the age of onset histogram showed a bimodal age of onset distribution, in this case with an inflection point at age 4 years (Supplementary Figure 1, available with the online version of this article). Therefore, we analyzed separately children with onset before as compared to after their fourth birthday. In 260 (72.02%) patients, symptoms started at ≤ 4 years. Compared to children

with early onset disease, those with onset > 4 years were more often male, with sacroiliitis, psoriasis, and enthesitis, but less uveitis, dactylitis, and ANA positivity. Older children were more likely to receive treatment with daily NSAID, but less likely to receive GC (Table 1).

Application of formal classification criteria. Applying the ILAR algorithm for JPsA diagnosis to the entire CARRA JIA cohort (6404 patients) revealed 318 children who fulfilled the criteria. The vast majority, 256 patients (80.5%), were defined as having JPsA by their treating rheumatologist and were included in the CARRA-JPsA cohort (Table 4).

Among the CARRA JIA patients, 268 children fulfilled CASPAR criteria for PsA; the majority [216 patients (80.6%)] were included in the CARRA-JPsA cohort (Table 4). Similar to findings with the ILAR algorithm, patients fulfilling CASPAR criteria for PsA in the CARRA-JPsA cohort had more nail pitting, dactylitis, and psoriasis, less uveitis, and did not differ in the prevalence of enthesitis, sacroiliitis, radiographic evidence of joint damage, or HQ score compared to children in the CARRA-JPsA cohort who did not fulfill either algorithm (Tables 5 and 6).

Of 52 patients who were not classified as JPsA by their treating physicians but would be considered as having PsA according to CASPAR criteria, fewer had psoriasis but more had enthesitis, sacroiliitis, IBD, and uveitis. This group reported worse scores on HQ questionnaires, compared to the group that fulfilled CASPAR criteria within the JPsA cohort (Table 6).

DISCUSSION

The CARRA-JPsA cohort studied here represents 5.6% of the JIA population in the CARRA legacy registry, in line with published data for prevalence of this subtype within

Table 2. Followup data. Results reported as n/total (%) unless otherwise indicated.

Variable	Enrollment (222 Patients)	Followup (222 Patients)	p
No arthritis		98/204 (48)	< 0.0001
Oligoarthritis	78/204 (38.2)	85/204 (41.7)	< 0.0001
Polyarthritis	126/204 (61.8)	21/204 (10.3)	< 0.0001
Nail pitting	70 (35.9%)	31/207 (15)	< 0.0001
Dactylitis	60 (30.9%)	5/208 (2.4)	< 0.0001
Psoriasis	137 (68.2%)	73/210 (34.8)	< 0.0001
Enthesitis	57 (29.5%)	17/210 (8.1)	< 0.0001
Sacroiliitis	35 (18.1%)	13/210 (6.2)	< 0.0001
IBD		1/187 (0.5)	
Uveitis	27 (15.1%)	8/187 (4.3)	< 0.0001
Imaging evidence of joint damage	47 (27.5%)	40/207 (19.3)	NS
HRQOL*	2.14 \pm 0.88, 2 (1–5)	2.13 \pm 0.83, 2 (1–5)	NS
Parent/subject overall well-being score*	2.33 \pm 2.20, 1 (0–9)	2.30 \pm 2.36, 2 (0–9)	NS
Parent/subject pain scale score*	2.58 \pm 2.64, 1 (0–10)	2.23 \pm 2.39, 1 (0–8)	NS
CHAQ*	0.34 \pm 0.48, 0.13 (0–2.63)	0.29 \pm 0.49, 0.0 (0–3.0)	NS
PGA*	1.50 \pm 1.71, 1 (0–8)	1.19 \pm 1.5, 1 (0–7)	NS

* Results are mean \pm SD, median (range). IBD: inflammatory bowel disease; HRQOL: health-related quality of life; CHAQ: Childhood Health Assessment Questionnaire; PGA: physician's global assessment; NS: nonsignificant.

Table 3. Followup data on improvement in objective findings (Model 1) and HQ scores (Model 2). Data are n (%) unless otherwise indicated.

Variable	Univariate Model		Multivariable Logistic Regression Model		
Model 1: Objective outcomes*	Improved < 5 (43 pts)*	Improved ≥ 5 (130 pts)*	p	p	OR (95% CI)
Age at onset, yrs, mean ± SD	9.25 ± 4.02	7.34 ± 4.64	0.018	0.04	0.91 (0.84–0.99)
Ethnicity: not Hispanic or Latino	41 (95.3)	114 (87.7)	NS		
Race: white	39 (90.7)	119 (75.3)	NS		
Sex, female	17 (39.5)	93 (71.5)	< 0.0001	0.001	3.43 (1.64–7.17)
DMARD	29 (69.0)	77 (59.7)	NS		
bDMARD	25 (59.5)	65 (50.0)	NS		
GC	8 (19.0)	23 (17.7)	NS		
Daily NSAID	17 (40.5)	43 (33.3)	NS		
Model 2: HQ outcomes**	Not Improved in All (163 pts)**	Improved All (11 pts)**	p	p	OR (95% CI)
Age at onset	7.98 ± 4.62	7.12 ± 4.31	NS		
Ethnicity: not Hispanic or Latino	147 (90.2)	11 (100)	NS		
Race: white	152 (93.3)	10 (90.9)	NS		
Sex, male	59 (36.2)	6 (54.5)	NS		
Psoriasis	111 (69.4)	8 (72.7)	NS		
Nail pitting	53 (33.8)	7 (63.6)	0.056	0.13	2.75 (0.74–10.18)
Dactylitis	43 (27.7)	3 (27.3)	NS		
Enthesitis	42 (27.1)	7 (63.6)	0.016	0.03	4.14 (1.12–15.25)
Sacroiliitis	26 (16.7)	3 (27.3)	NS		
Oligoarthritis	57 (35)	4 (40.0)	NS		
Polyarthritis	106 (65)	6 (60)	NS		
DMARD	102 (63.0)	6 (54.5)	NS		
bDMARD	82 (50.3)	7 (63.6)	NS		
GC	29 (17.8)	3 (27.3)	NS		
Daily NSAID	60 (37.0)	3 (27.3)	NS		

Model 1: Objective outcomes*: psoriasis, nail pitting, dactylitis, arthritis, enthesitis, and sacroiliitis. Improved in < 5 from the following variables: psoriasis, nail pitting, dactylitis, arthritis, enthesitis, and sacroiliitis. Improved in ≥ 5 from the following variables: psoriasis, nail pitting, dactylitis, arthritis, enthesitis and sacroiliitis. Model 2: Health questionnaire (HQ) outcomes**: 4 HQ (PAINSC, HRQOL, GLASWBSC, and PGA). Improved in < 4 HQ (PAINSC, HRQOL, GLASWBSC, and PGA). Improved in all 4 HQ (PAINSC, HRQOL, GLASWBSC, and PGA). NS: nonsignificant; PGA: physician global assessment; DMARD: disease-modifying antirheumatic drug; GC: glucocorticosteroids; NSAID: nonsteroidal antiinflammatory drugs; bDMARD: biologic DMARD; HRQOL: health-related quality of life; PAINSC: parent/subject pain scale; GLASWBSC: parent/subject overall well-being.

Table 4. Distribution of patients fulfilling ILAR and CASPAR criteria for psoriatic arthritis in the CARRA database.

JIA Category in CARRA Database	ILAR-JPsA (% ILAR final)*	CASPAR-JPsA (% final CASPAR)**
Enthesitis-related arthritis	10 (3.1)	13 (4.9)
Juvenile ankylosing spondylitis		1 (0.4)
Oligoarthritis extended	3 (0.9)	2 (0.7)
Oligoarthritis persistent	19 (6.0)	13 (4.9)
Polyarthritis RF-negative	25 (7.9)	15 (5.6)
Polyarthritis RF-positive	1 (0.3)	0 (0)
CARRA-JPsA	256 (80.5)	216 (80.6)
Systemic JIA		3 (1.1)
Undifferentiated arthritis	4 (1.3)	4 (1.5)
Other		1 (0.4)
Total	318 (100)	268 (100)

* Children fulfilling ILAR criteria for JPsA in the CARRA JIA database.
 ** Children fulfilling CASPAR criteria for PsA in the CARRA JIA database.
 ILAR: International League of Associations for Rheumatology; CASPAR: Classification criteria for Psoriatic Arthritis; CARRA: Childhood Arthritis and Rheumatology Research Alliance; JIA: juvenile idiopathic arthritis; JPsA: juvenile psoriatic arthritis; RF: rheumatoid factor.

JIA^{5,12,13,14}. Data on this cohort were analyzed in light of current knowledge and understanding of PsA from both pediatric and adult rheumatology literature using the ILAR and CASPAR classification criteria.

A bimodal age of onset has been reported in children with JPsA^{4,14,15}, similar to the well-recognized yet poorly understood demographic feature of all JIA, which has 1 peak age of onset at 2–3 years and a second peak in mid-adolescence¹⁶. Our findings are consistent with the literature pointing to a female predominance in early-onset JPsA, and increased incidence of sacroiliitis in later-onset JPsA. Stoll and Punaro observed that patients with early-onset JPsA had features similar to ANA-positive oligoarticular and polyarticular JIA, including more females and presence of chronic uveitis, whereas older children had features of SpA¹⁴. The better outcome observed in females with early arthritis onset may be explained in part by the inclusion of females with oligoarticular arthritis, who in general have a more mild disease¹⁷.

The influence of age and sex on disease expression, which is also observed in adults with PsA, likely has a genetic

Table 5. ILAR algorithm applied to the CARRA-JPsA cohort. Data are n (%) unless otherwise indicated.

Variables	CARRA-JPsA Cohort		p*
	ILAR-negative, 105 Patients	ILAR-positive, 256 Patients	
Subject age at enrollment, yrs, mean ± SD	12.25 ± 4.20	13.21 ± 4.04	0.044
Subject age at onset of symptoms, yrs, mean ± SD	7.61 ± 4.49	8.52 ± 4.62	NS
Subject age first rheumatologist, yrs, mean ± SD	8.64 ± 4.34	9.66 ± 4.60	0.06
Ethnicity: not Hispanic or Latino	91 (86.7)	240 (93.8)	0.027
Race: white	98 (93.3)	241 (94.1)	NS
Sex: male	42 (40.0)	95 (37.1)	NS
Family history of psoriasis	31 (29.5)	82 (32.0)	NS
HRQOL, mean ± SD, median (range)	2.18 ± 0.88, 2 (1–4)	2.16 ± 0.83, 2 (1–5)	NS
Parent/subject overall well-being score, mean ± SD, median (range)	2.17 ± 2.23, 1 (0–9)	2.40 ± 2.19, 2 (0–9)	NS
Parent/subject pain scale score, mean ± SD, median (range)	2.69 ± 3.02, 2 (0–10)	2.54 ± 2.47, 2 (0–10)	NS
CHAQ score, mean ± SD, median (range)	0.42 ± 0.56, 0.13 (0–2.63)	0.31 ± 0.44, 0.13 (0–2.63)	NS
PGA, mean ± SD, median (range)	1.79 ± 1.88, 1 (0–8)	1.38 ± 1.63, 1 (0–8)	NS
Oligoarthritis ever	52 (51)	108 (42.2)	NS
Polyarthritis ever	50 (49.0)	148 (57.8)	NS
No. currently active joints, mean ± SD, median (range)	2.09 ± 4.20, 1 (0–32)	1.58 ± 2.58, 0 (0–12)	NS
Nail pitting ever	22 (23.4)	106 (42.9)	0.001
Dactylitis	20 (20.6)	82 (33.2)	0.022
Psoriasis ever	10 (10.7)	223 (87.5)	0.0001
Enthesitis ever	37 (38.9)	75 (30.3)	NS
Sacroiliac joint tenderness ever	14 (14.9)	43 (17.3)	NS
IBD	1 (1.1)	4 (1.6)	NS
Uveitis	17 (17.3)	22 (8.8)	0.023
ACPA	5 (11.9)	2 (2.1)	0.029
RF	3 (2.9)	14 (5.5)	NS
ANA	38 (36.2)	97 (37.9)	NS
HLA-B27-positive	14 (19.2)	12 (6.9)	0.004
Imaging evidence of joint damage	27 (30.3)	47 (22.2)	NS
Imaging evidence of active sacroiliitis	3 (30)	5 (18.5)	NS

* Specific values for $p \leq 0.05$ are reported; p value ≤ 0.007 after adjustment for multiple comparisons between patients in the JPsA cohort who fulfill ILAR criteria (ILAR-positive) and those who do not (ILAR-negative). ILAR: International League of Associations for Rheumatology; CARRA: Childhood Arthritis and Rheumatology Research Alliance; JPsA: juvenile psoriatic arthritis; RF: rheumatoid factor; HRQOL: health-related quality of life; CHAQ: Childhood Health Assessment Questionnaire; PGA: physician's global assessment; NS: nonsignificant; IBD: inflammatory bowel disease; ACPA: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; ANA: antinuclear antibody test.

basis^{18,19,20}. Adult patients with early-onset PsA (onset age < 40 yrs) typically have a longer psoriasis-arthritis latency period, a family history of disease, severe psoriasis, enthesitis, and oligoarthritis²¹. Additional studies point to more frequent axial involvement in males¹⁸, whereas presence of polyarthritis correlates positively with age and female sex^{19,22}. Taken together with these results, our data suggest an overall pattern in which JPsA presents in childhood (at ≤ 4 –6 yrs) as predominantly a disease of females with peripheral arthritis, followed by presentation of later-onset JPsA (> 4–6 yrs) and early PsA with enthesial and axial involvement, more common in males, and then a later presentation again with more tendency for peripheral arthritis. The precise inflection point varies by the study and is subject to errors in symptom recall. One interpretation is that later-onset

JPsA is an early presentation of early-onset adult PsA disease. It is also possible that early-onset “JPsA” is a subset of early-onset (nonsystemic) JIA as a whole, rather than a discrete subset of JPsA. Further studies of the JPsA population are needed for a better understanding of the influence of age and sex on the clinical manifestations of the disease. It will be interesting to compare data from the young onset subgroup with the like-aged patients with JIA, in the CARRA registry and in other datasets.

CARRA-JPsA patients in our cohort tended to have less psoriasis compared with adult patients, in whom psoriasis will precede or be diagnosed at the time of arthritis in 85% of patients²³. This observation was made in other JPsA cohorts as well^{4,5}. A possible explanation is that, in contrast to adults with PsA, psoriasis in JPsA often occurs years after

Table 6. CASPAR algorithm applied to the CARRA-JPsA cohort and to the CARRA-JIA cohort. Data are n (%) unless otherwise indicated.

Variables	CARRA-JPsA Cohort, 361 Patients			JIA Cohort, 6043 Patients	
	CASPAR-negative, 145 Patients	CASPAR-positive, 216 Patients	p*, JPsA Cohort	CASPAR-positive, 52 Patients	p, CASPAR-positive**, JPsA+ vs JPsA-
Subject age at enrollment, yrs, mean ± SD	12.72 ± 4.41	13.07 ± 3.89	NS	13.00 ± 4.42	NS
Subject age at onset of symptoms, yrs, mean ± SD	8.0 ± 4.47	8.44 ± 4.68	NS	6.02 ± 3.79	0.001
Subject age first rheumatology visit, yrs, mean ± SD	9.13 ± 4.35	9.53 ± 4.67	NS	7.63 ± 4.30	0.013
Time between symptom onset and first rheumatology visit, yrs, mean ± SD	1.09 ± 1.49	1.00 ± 1.44	NS	1.53 ± 1.88	NS
Ethnicity: not Hispanic or Latino	130 (89.7)	201 (93.1)	NS		NS
Race: white	109 (91.6)	158 (91.3)	NS	38 (86.4)	NS
Sex: male	53 (36.6)	84 (38.9)	NS	20 (12.7)	NS
Family history of psoriasis	50 (34.5)	63 (29.2)	NS	15 (28.8)	NS
HRQOL, mean ± SD	2.23 ± 0.83	2.13 ± 0.85	NS	2.35 ± 0.71	NS
Parent/subject overall well-being score, mean ± SD	2.33 ± 2.23	2.33 ± 2.19	NS	3.48 ± 2.45	0.001
Parent/subject pain scale score, mean ± SD	2.72 ± 2.93	2.49 ± 2.43	NS	3.42 ± 2.35	0.006
CHAQ score, mean ± SD	0.40 ± 0.54	0.3 ± 0.44	NS	0.55 ± 0.66	0.005
PGA, mean ± SD	1.61 ± 1.80	1.42 ± 1.66	NS	2.0 ± 2.15	NS
Oligoarthritis	71 (49.3)	89 (41.6)	NS	23 (44.2)	NS
Polyarthritits	73 (50.7)	125 (58.4)	NS	29 (55.8)	NS
Nail pitting ever	18 (13.5)	110 (52.9)	< 0.0001	34 (65.4)	NS
Dactylitis	18 (13.3)	84 (40.2)	< 0.0001	22 (44.9)	NS
Psoriasis ever	50 (37.3)	183 (85.1)	< 0.0001	32 (65.3)	0.001
Enthesitis ever	46 (34.6)	66 (31.5)	NS	28 (54.9)	0.002
Sacroiliac joint tenderness ever	23 (17.1)	34 (16.4)	NS	21 (40.4)	0.0001
IBD	2 (1.5)	3 (1.4)	NS	11 (21.2)	0.0001
Uveitis	22 (15.9)	17 (8.1)	0.023	13 (25)	0.001
ACPA	5 (10)	2 (2.3)	NS	0 (0)	NS
RF	5 (3.4)	12 (5.6)	NS	1 (1.9)	NS
ANA	55 (46.2)	80 (46.2)	NS	18 (40.9)	NS
HLA-B27-positive	11 (11.7)	15 (9.9)	NS	7 (19.4)	NS
Imaging evidence of joint damage	32 (26)	42 (23.6)	NS	15 (33.3)	NS
Imaging evidence of active sacroiliitis	4 (28.6)	4 (17.4)	NS	2 (22.2)	NS

* Specific values for $p \leq 0.05$ are reported. P value ≤ 0.008 adjusted for multiple comparison, comparing in the JPsA cohort between patients who fulfill CASPAR criteria (CASPAR+) with those who do not (CASPAR-). ** Specific values for $p \leq 0.05$ are reported. P value ≤ 0.015 adjusted for multiple comparison, comparing children fulfilling CASPAR criteria (CASPAR+) in the JPsA cohort (JPsA+) to those who fulfill CASPAR but were not in the JPsA cohort (JPsA-). CASPAR: Classification criteria for Psoriatic Arthritis; CARRA: Childhood Arthritis and Rheumatology Research Alliance; JPsA: juvenile psoriatic arthritis; JIA: juvenile idiopathic arthritis; HRQOL: health-related quality of life; PGA: physician's global assessment; ACPA: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; ANA: antinuclear antibody test; CHAQ: Childhood Health Assessment Questionnaire; NS: nonsignificant; IBD: inflammatory bowel disease.

arthritis onset^{5,24,25}, and its development may be obscured by DMARD treatment, as has been suggested for uveitis associated with JIA²⁶. Only 37% in our CARRA-JPsA cohort report nail involvement, compared with 57% in previous JPsA studies^{2,5,15} or 66% in adults²⁷. The prevalence of dactylitis in our cohort (29.7%) is similar to the report of Butbul Aviel, *et al*², but lower compared with older reports^{5,15}. The prevalence of enthesitis and uveitis in our cohort are in the range (14%–45%) of published series^{2,4}.

Axial involvement, documented as sacroiliitis/IBP in the CARRA-JPsA cohort, was found in 16.7%, and axial changes were found in 21.6% of those who had radiographic imaging. Pediatric and adult literature point to asymptomatic axial involvement in patients with psoriasis and to axial

radiographic features of SpA^{15,28,29}. There was no correlation between HLA-B27 positivity and radiographic or clinical findings of sacroiliitis, in line with a report on PsA³⁰.

At enrollment, an average 4.6 years after symptom onset, 24.6% of patients in the CARRA-JPsA cohort had radiographic evidence of joint damage, similar to findings reported by Southwood, *et al* in 1989⁵. However, taking into consideration the bDMARD prescribed to 52.9% of our cohort, these results are a cause for concern and point to the aggressive nature of the disease. Supporting this idea, Kane, *et al* described erosive changes after 2 years of followup in 47% of patients with early PsA, despite treatment with DMARD³¹. The use of DMARD in our CARRA-JPsA cohort is in line with that reported in the registry as a whole³².

The prevalence of ANA positivity in our cohort is similar to that found in other JPsA studies^{2,4,5,15} and series in PsA^{33,34}. RF positivity (4.7%) in our cohort is also found in PsA³⁵, although ACPA positivity is lower, 1.9% vs 10.6%^{36,37}. Differences in laboratory methods may have confounded these results.

Our findings documenting improvement in objective findings are supported by Butbul Aviel, *et al*, whose study was also performed in the era of bDMARD and found the median time to inactive disease while taking therapy was 1.23 years². To our knowledge, only 1 study to date has addressed longterm prognosis in JPsA. Of 31 patients followed for ≥ 15 years, 55% were in remission without medication for ≥ 12 months; however, 33% had active disease requiring DMARD treatment³. Our observation of a favorable prognosis in females with younger age at disease onset is not supported by others^{2,4}. Possible explanations include the short (1-yr) followup in our study and differences in study populations^{2,4}. The potential of PsA to cause impaired well-being and function beyond objective variables³⁸ was demonstrated in our CARRA-JPsA cohort. This finding is similar to findings in PsA in which a high prevalence of fibromyalgia was observed³⁹. In our dataset at followup, objective improvements were not accompanied by improvements in HQ scores, although this may be in part because HQ scores consistent with overall good status already were registered at baseline.

The 19.5% of our CARRA-JPsA cohort whose disease manifestations did not fulfill ILAR criteria tended to have fewer classical manifestations of psoriasis, dactylitis, and nail pitting. Because psoriatic skin rash may manifest years after arthritis onset in children⁵, these findings may reflect the physician's suspicion that PsA was the appropriate diagnosis, based on the presence of SpA and consequently, less strict application of ILAR criteria, by which those children would be assigned to ERA or undifferentiated JIA⁴⁰. The CASPAR classification criteria for PsA⁷ are likely to be useful as diagnostic criteria⁴¹. Applying those criteria to the CARRA legacy registry, the JIA cohort identified 52 additional patients who would be classified as PsA by adult rheumatologists. Those patients had less psoriasis but more enthesitis, IBP, IBD, and uveitis, all manifestations of the spondyloarthritis⁴⁰. Findings of asymptomatic enthesitis in patients with JPsA and PsA provide additional support for this concept^{42,43}.

Although some differences we report may reflect semantic differences in disease classification, they have therapeutic implications. Because certain traditional DMARD appear to be less effective in PsA compared with RA, whereas newer biologics — particularly those targeting interleukin 17 — appear to be more effective in psoriatic disease⁴⁴, patients who are not classified as having JPsA by pediatric rheumatologists — versus those labeled as having JPsA/PsA — might be offered different treatment options as new medications become available. Psoriasis, which often occurs after

arthritis in children and may also be prevented by use of DMARD, does not serve as a reliable indicator. Further research on the immunology, pathogenesis, and genetics of these clinically related conditions may provide the biologic information needed for a more precise classification scheme⁴⁵.

Several limitations of our study should be noted. Our analyses were retrospective using classification criteria. Information on anterior versus posterior uveitis was not available, and articular involvement was recorded as oligoarthritis and polyarthritis, not number of involved joints. Information on the extent of arthritis during 1 year of disease, but not at onset, was collected, limiting our ability to compare JPsA subgroups defined by oligoarticular and polyarticular disease. Radiographic data were not interpreted centrally, and lacked specific information, such as the type of imaging performed. Thus, our algorithm assigned points for CASPAR criteria without the radiographic component; notably, however, this criterion is the least frequently used when the CASPAR criteria are applied⁷. In the implementation of the ILAR criteria we excluded children having uveitis, because the CARRA registry does not distinguish between acute and chronic uveitis. Therefore, underestimation of the ILAR-JPsA and CASPAR-JPsA cohorts could have occurred.

Our analysis of data on the physician-diagnosed CARRA-JPsA cohort in the CARRA legacy registry supports the division of this condition into 2 subgroups, according to the age of onset. After 1 year of followup, a significant improvement was noted in objective findings, but without improvement in HQ scores. We suggest that pediatric and adult rheumatologists should be familiar with the differences in their approaches; adult rheumatologists should be aware that they may be inheriting a number of patients with PsA (per CASPAR criteria) who might be labeled differently by their pediatric colleagues. Applying CASPAR criteria across the age spectrum would likely enhance continuity of care and better reflect current concepts about PsA pathogenesis and expression. This suggestion requires discussion and validation by a panel of experts in pediatric and adult rheumatology.

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APPENDIX

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