The Systemic Juvenile Idiopathic Arthritis Cohort of the Childhood Arthritis and Rheumatology Research Alliance Registry: 2010–2013

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ABSTRACT. ***Objective.*** We aimed to identify the (1) demographic/clinical characteristics, (2) medication usage trends, (3) variables associated with worse disease activity, and (4) characteristics of patients with persistent chronic arthritis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry's systemic juvenile idiopathic arthritis (sJIA) cohort.

Methods. Demographics, disease activity measures, and medications at enrollment of patients with sJIA in the CARRA Registry were analyzed using descriptive statistics. Multivariate analyses were conducted to identify associations with increased disease activity. Medication usage frequencies were calculated by year.

Results. There were 528 patients with sJIA enrolled in the registry (2010–2013). There were 435 patients who had a complete dataset; of these, 372 met the International League of Associations for Rheumatology criteria and were included in the analysis. At enrollment, median disease duration and joint count were 3.7 years and 0, respectively; 16.4% had a rash and 6.7% had a fever. Twenty-six percent were taking interleukin 1 (IL-1) inhibitors and 29% glucocorticoids. Disease-modifying antirheumatic drugs and tumor necrosis factor inhibitors use decreased, while IL-6 inhibitor use increased between 2010 and 2013. African American patients had worse joint counts ($p = 0.003$), functional status ($p = 0.01$), and physician's global assessment ($p = 0.008$). Of the 255 subjects with > 2 years of disease duration, 56% had no arthritis or systemic symptoms, while 32% had persistent arthritis only.

Conclusion. Most patients in the largest sJIA cohort reported to date had low disease activity. Practice patterns for choice of biologic agents appeared to change over the study period. Nearly one-third had persistent arthritis without systemic symptoms > 2 years after onset. African Americans were associated with worse disease activity. Strategies are needed to improve outcomes in subgroups with poor prognosis. (First Release June 15 2016; J Rheumatol 2016;43:1755–62; doi:10.3899/jrheum.150997)

Key Indexing Terms:
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS EPIDEMIOLOGY TREATMENT

Systemic juvenile idiopathic arthritis (sJIA) is a rare and potentially fatal disease distinguished by systemic features in addition to arthritis. Before the availability of biologic agents, many children developed joint damage, growth disturbance, and severe disability. Macrophage activation syndrome (MAS), a life-threatening disease complication, occurs in about 10% of children with reported mortality rates ranging from 8–22%[1,2]. The rarity of sJIA makes meaningful research challenging, as do the phenotypic heterogeneity and the lack of a precise diagnostic test for sJIA.

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The International League of Associations for Rheumatology (ILAR) classification criteria for sJIA is at least 6 weeks of arthritis in the setting of a quotidian (daily) fever greater than 39°C for at least 2 weeks with at least 1 of the following: rash, lymphadenopathy, serositis, or organomegaly[3]. Children meeting these criteria often fall into 2 distinct phenotypes (systemic-feature predominant or arthritis predominant), which may change during the disease course. Although the disease course can also be monocyclic or polycyclic, more than 50% of children in the prebiologic era followed a chronic, persistently active disease course[4]. Identifying characteristics associated with a more severe disease course may aid in recognition of patients who require more aggressive treatment regimens.

Treatment of sJIA has traditionally incorporated nonsteroidal antiinflammatory drugs (NSAID), glucocorticoids (GC), disease-modifying antirheumatic drugs (DMARD), and in the last decade, biologic agents. Biologic agents [specifically interleukin 1 (IL-1) and IL-6 inhibitors] have greatly improved short-term outcomes for many patients with sJIA[5,6,7,8,9]. Studies of treatment with IL-1 and IL-6 inhibitors showed excellent responses, with significant steroid-sparing benefits and potentially improved prognosis[8,9,10].

The Childhood Arthritis and Rheumatology Research Alliance (CARRA), supported by a grant from the National Institutes of Health, began the CARRA Registry in 2010 (now called the CARRA Legacy Registry to distinguish it from the newly established CARRA Registry, which began enrollment in 2015) to address outstanding questions in pediatric rheumatic diseases[11]. A study by Beukelman, *et al* used the CARRA Legacy Registry data from 2010–2011 to describe medication use for all subtypes of JIA[12]. Of 246 children with sJIA, more than half (65%) had received a biologic agent and 87% had been treated with methotrexate (MTX) or cyclosporine during their course. Tocilizumab (TCZ) in 2011 became the first biologic medication for the treatment of sJIA approved by the US Food and Drug Administration (FDA), followed by canakinumab in 2013. The availability of these new, effective drugs for sJIA is likely affecting treatment patterns, but this has not been previously described.

The optimal treatment for individual patients remains uncertain[13]. A CARRA-wide survey to develop consensus treatment plans (CTP) for sJIA showed that treatment patterns are quite variable among pediatric rheumatologists in the network[14]; the most common treatments were GC, MTX, IL-1 inhibitors, IL-6 inhibitors, and tumor necrosis factor-α (TNF-α) inhibitors.

From May 2010 to December 2013, almost 9450 children with rheumatic diseases, including 6490 (69%) with all categories of JIA and 528 (6%) with sJIA, were enrolled in the CARRA Legacy Registry, creating the largest sJIA cohort to date. Clinical data from this cohort offer a unique opportunity to study demographic characteristics, disease phenotypes, current treatment patterns, and factors associated with more severe disease. To our knowledge, previous large studies looking at JIA demographics analyzed populations outside North America, did not focus on sJIA, and were predominantly retrospective[15,16,17,18,19].

The primary goals of our current study were to identify (1) demographic/clinical characteristics, (2) medication usage trends, (3) variables associated with worse disease activity, and (4) characteristics of patients with persistent chronic arthritis in the CARRA Legacy Registry sJIA cohort.

MATERIALS AND METHODS

Since 2010, data on children with major pediatric rheumatic diseases were collected through the CARRA Registry from 62 sites in the United States and Canada. The cohort is a convenience sample of patients at participating clinical sites. Thus, patients could be enrolled at any time during their disease course. Institutional Review Board approval was obtained prior to the commencement of data collection.

Diagnosis of sJIA was determined by the treating physician. Registry enrollment guidelines specified that patients should fulfill the published ILAR criteria for JIA. To be included in the analyses reported here, a complete dataset, as defined by the study team, was required at the time of enrollment visit (EV): sex, age at baseline, age at onset, year of onset, age first seen by a pediatric rheumatologist, site of enrollment, disease duration, ethnicity, race, family history of autoimmune disease, physician's global assessment [PGA; visual analog scale (VAS)], American College of Rheumatology (ACR) functional status, joint count, history of or current systemic features (fever, rash, lymphadenopathy, hepatosplenomegaly, serositis), and medication exposures. Patient-reported measures including overall well-being (VAS), health-related quality of life (HRQOL) rating (categorical scale ranging from 1–5), pain VAS or Faces Pain Scale–Revised score depending on child age, and the Childhood Health Assessment Questionnaire (CHAQ) score were also required for inclusion. Those who did not meet the strict ILAR criteria were excluded from our analysis, and a comparison of the 2 groups (those meeting criteria and those not) was performed, looking for any significant differences in demographic or clinical features.

To assess trends in treatment practices over the study period, information on medication use was collected for all patients at the EV, including use of NSAID, GC, DMARD, and biologics. Previous or current medications were collected, but medication dosage, start, and stop dates were not. For the analysis of medication use, biologic agents were grouped as follows: (1) IL-1 inhibitor (anakinra, canakinumab, rilonacept), (2) IL-6 inhibitor (TCZ), (3) TNF-α inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab), and (4) other [abatacept (ABA), intravenous immunoglobulin (IVIG), rituximab (RTX), other]. Frequency of current usage of each medication class at EV was analyzed for each calendar year and p values for trend over time were calculated using the chi-square analysis.

Multivariate analysis was performed in those with disease duration > 6 months at EV looking for patient characteristics associated with increased disease activity. Joint count was analyzed with a general linear model, assuming a negative binomial distribution. ACR status and HRQOL were analyzed using multiple logistic regression, assuming an ordered categorical response. PGA, overall well-being, pain score, and CHAQ were analyzed with a general linear model, assuming an ordered multinomial distribution. Systemic features were analyzed with multiple logistic regression, assuming a dichotomous response. Analysis was performed using the SAS Institute software.

Finally, patients with disease duration of > 2 years were divided into 4 subgroups: those with persistent arthritis despite absence of systemic symptoms, those with both persistent arthritis and systemic symptoms, those with systemic symptoms without arthritis, and those with neither arthritis

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nor systemic symptoms. Those with persistent arthritis in the absence of systemic symptoms were compared with the remainder of the cohort with a disease duration of > 2 years.

RESULTS

There were 528 children enrolled in the CARRA Registry with a diagnosis of sJIA. Of those, 435 patients (82%) from 54 sites had a complete dataset. Upon data review, 372 (71%) of these patients met the ILAR criteria and were included in the EV analysis. The demographic characteristics at EV are shown in Table 1. Median disease duration for the cohort meeting the ILAR criteria was 3.7 years. Of those patients, 15% (n = 56) had a disease duration of < 6 months at the EV.

Of the 63 patients who did not meet the ILAR criteria, 20 (32%) had fever and arthritis only, 6 (9.5%) had fever and systemic features but no arthritis, 36 (57%) had arthritis but no reported fever that met the ILAR criteria (although 10 had at least 1 systemic feature), and 1 did not fulfill the ILAR fever or arthritis criteria. Table 2 shows that there were no significant differences in disease activity and demographic characteristics at EV between those who met the ILAR criteria and those who did not. Only those meeting the ILAR criteria were included in the analysis that follows.

Disease activity, pain, and functional status. Disease activity of the group as a whole at EV was low (Table 3). Most patients did not have active systemic symptoms, with rash in only 61 patients (16%) and fever in 25 (7%). The median active joint count was 0 [interquartile range (IQR) 0.0–2.0]. PGA was low (median 1.0, IQR 0–3). Only 25 patients (7%) reported poor/very poor HRQOL. Assessment of overall well-being by parents/patients indicated that patients were doing well (median 2.0, IQR 0–5). Of note, only 25 (7%) had the worst ACR functional classes of III or IV at EV, despite 206 (60% of those with data reported) reporting having had an ACR class of III or IV at some point during their disease course.

Medication usage at EV. At EV, 109 (29%) were taking either pulse or oral GC, 198 (53%) non-biologic DMARD (46% of

Table 1. Demographic data. Values are n (%) or median (interquartile range).

Variables	Met ILAR Criteria, n = 372	CARRA Legacy Systemic JIA Cohort, n = 528
Male	173 (46.5)	237 (44.9)
Non-Hispanic	325 (87.4)	460 (87.1)
Race		
White	296 (79.6)	403 (76.3)
African American	37 (9.9)	61 (11.6)
Other	39 (10.5)	59 (11.2)
Age at onset, yrs	4.6 (2.3–9.4)	4.7 (2.3–9.3)
Disease duration, yrs	3.7 (1.1–7.5)	3.9 (1.1–7.7)
Onset calendar yr	2008 (2004–2010)	2008 (2004–2010)

ILAR: International League of Associations for Rheumatology; CARRA: Childhood Arthritis and Rheumatology Research Alliance; JIA: juvenile idiopathic arthritis.

Table 2. ILAR criteria groups. Those without data were excluded from analysis. Values are n (%) or median (interquartile range) unless otherwise specified.

Variables	Did Not Meet ILAR Criteria, Total n = 63	Met ILAR Criteria, Total n = 372	p
Male	24 (38.1)	173 (46.5)	0.2
Non-Hispanic	56 (89.8)	325 (87.2)	0.7
Race			
White	46 (73)	296 (79.6)	0.5
African American	8 (12.7)	37 (10)	
Other	9 (14.3)	39 (10.5)	
Worst ACR category*	Total n = 46	Total n = 206	
1	10 (15.9)	49 (13.2)	0.32
2	13 (20.6)	86 (23.1)	
3	13 (20.6)	90 (24.2)	
4	10 (15.9)	116 (31.2)	
Systemic features, present	8 (12.7)	71 (19.1)	0.22
Age at onset, yrs	4.7 (2.4–9.1)	4.6 (2.3–9.4)	0.7
Disease duration, yrs	4.1 (1.6–7.6)	3.7 (1.1–7.5)	0.7
Onset calendar yr	2007 (2004–2010)	2008 (2004–2010)	0.9
Overall well-being score, 0–10 VAS	2 (1–5)	2 (0–5)	0.6
Pain score, 0–10 VAS	2 (0–6)	1 (0–5)	0.4
CHAQ score	0.12 (0–0.62)	0.13 (0–0.63)	0.8

* Does not include data for entire cohort because only "Current ACR category" was required for entry. ILAR: International League of Associations for Rheumatology; ACR: American College of Rheumatology; VAS: visual analog scale; CHAQ: Childhood Health Assessment Questionnaire.

Table 3. Disease characteristics at enrollment visit (n = 372). Values are n (%) or median (interquartile range).

Disease Characteristics	Values
Active systemic features at baseline visit	
Quotidian fever	25 (6.7)
Evanescent rash	61 (16.4)
Generalized lymphadenopathy	10 (2.7)
Hepato/splenomegaly	8 (2.2)
Serositis	7 (1.9)
No. currently active joints	0.0 (0.0–2.0)
HRQOL	
Excellent	85 (22.9)
Very good	129 (34.7)
Good	133 (35.7)
Poor	21 (5.6)
Very poor	4 (1.1)
Patient/caregiver overall well-being score	2.0 (0.0–5.0)
Patient/caregiver pain scale score	1.0 (0.0–5.0)
CHAQ score	0.1 (0.0–0.6)
PGA score	1.0 (0.0–3.0)
ACR functional class, current	
Class I	264 (76.3)
Class II	63 (16.9)
Class III or IV	25 (6.7)

HRQOL: health-related quality of life; CHAQ: Childhood Health Assessment Questionnaire; PGA: physician's global assessment; ACR: American College of Rheumatology.

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total cohort were taking MTX, with the remainder taking azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, mycophenolate mofetil, sulfasalazine, or tacrolimus). There were 195 children (52%) who were taking 1 or more biologic agents: 97 (26% of total cohort) an IL-1 inhibitor, 30 (8%) an IL-6 inhibitor, 65 (18%) a TNF-α inhibitor, and 12 (3%) "other" biologics, which included ABA, belimumab, IVIG, and RTX. Five children were receiving more than 1 biologic: 4 were taking an IL-1 inhibitor and a TNF-α inhibitor, and 1 was taking an IL-1 inhibitor plus ABA.

Of the patients, 57% whose disease duration was < 6 months at EV (n = 56) were receiving GC, 37.5% a DMARD, 25% an IL-1 inhibitor, and 5.4% an IL-6 inhibitor. There were no patients receiving TNF-α inhibitors in this subgroup.

Changes in medication use over study period. There were statistically significant differences in medication use when analyzed by year of visit, with DMARD and TNF-α inhibitor use decreasing substantially over the study period, while IL-6 inhibitor use increased (Figure 1). Use of GC remained stable over the study period. The changes in IL-1 inhibitor use were not statistically significant.

Patient characteristics associated with increased disease activity. In multiple regression models, African American race was the only patient characteristic consistently associated with worse disease status at EV. African American patients were more likely to have worse joint counts (OR 3.3, p = 0.003), ACR status (OR 2.9, p = 0.01), and PGA (OR 2.6, p = 0.008), but pain score, HRQOL, CHAQ, or overall well-being score were not significantly different. A race designation of "other" (not white or African American) was associated with better HRQOL and lower pain scores. Of note, there were no statistically significant differences in medication use by race.

In the analyzed group as a whole, prior TNF-α and IL-6 inhibitor use was associated with higher joint count (TNF OR 2.8, p = 0.001; IL-6 OR 3.7, p = 0.001), lower HRQOL (TNF OR 2.1, p = 0.0004; IL-6 OR 3.7, p = 0.001), and higher PGA (TNF OR 2, p = 0.006; IL-6 OR 2.4, p = 0.01). There were no statistically significant associations between disease duration at enrollment and measures of disease activity. Radiographic damage (defined as joint space narrowing, erosion, and/or ankyloses) reported at EV was associated with higher joint count (OR 2.1, p = 0.02) and higher PGA (OR 2.6, p = 0.002). Subjects who were older at disease onset also had worse CHAQ scores (OR 1.1, p = 0.003) and paradoxically, improved overall well-being scores (OR 1.1, p = 0.0009) and HRQOL (OR 1.1, p = 0.05).

Persistent arthritis subgroup. Among those patients in our analyses whose disease duration was > 2 years at EV (n = 255), 4 subgroups could be defined: those with both persistently active systemic features and arthritis (n = 19, 7.5%), those with systemic features only (n = 13, 5.1%), those with persistent arthritis only without systemic features (n = 81, 32%), and those with no active systemic disease or arthritis (n = 142, 56%). A subgroup analysis was performed looking

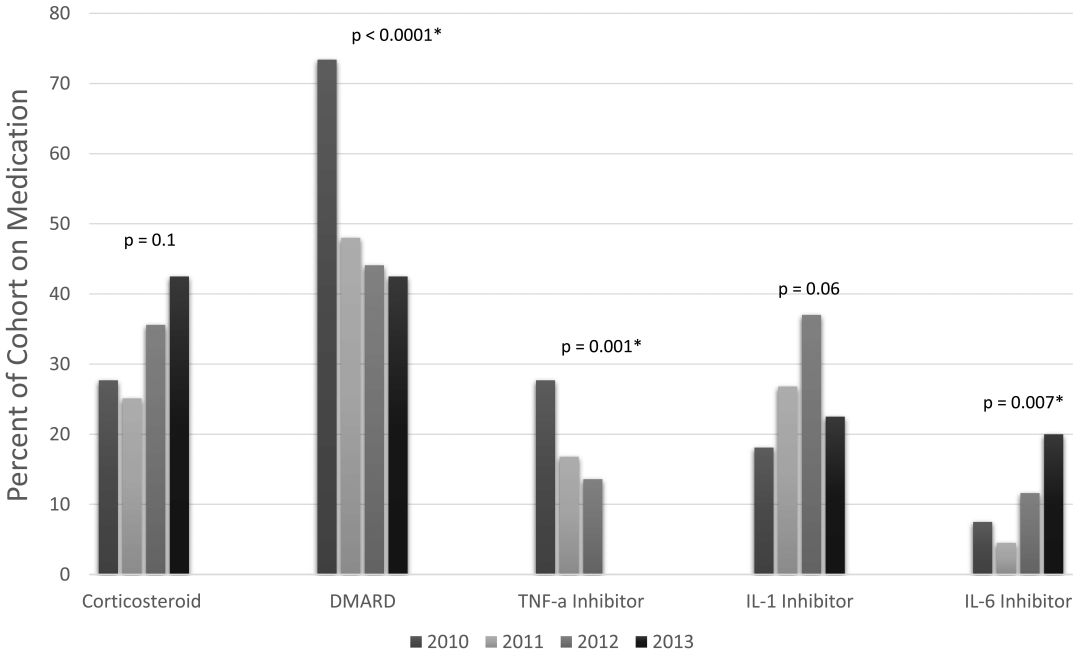

Figure 1. Medication at baseline visit over enrollment period. * The p values are a chi-square figure based on the change over time; p < 0.05 reflects a significant change in use over the 4-year study period. DMARD: disease-modifying antirheumatic drugs; TNF-α: tumor necrosis factor-α; IL-1: interleukin 1; IL-6: interleukin 6.

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at the group with persistent arthritis without systemic features compared with the remainder of the cohort. This revealed that there were significant differences based on race, with a higher percentage of African American patients (as compared with whites or other races) in the persistent arthritis-only subgroup, and a lower frequency of persistent arthritis among those who self-identified as one of the other races ($p = 0.045$). The persistent arthritis-only subgroup also appeared to have a shorter time from onset of symptoms to diagnosis ($p = 0.04$). There was no significant difference in age at diagnosis between the 2 groups, but those with persistent arthritis only had a longer duration of disease ($p < 0.001$). Medication use, particularly IL-6 inhibitor use, varied significantly between the groups, with 20% of those with persistent arthritis only having been receiving an IL-6 inhibitor (vs 4.6% in the comparator cohort, $p = 0.0001$). GC use was also significantly higher in the persistent arthritis-only subgroup (38% vs 14%, $p < 0.0001$), as was DMARD use (70% vs 47%, $p = 0.0005$). There was no significant difference in IL-1 inhibitor, TNF-α inhibitor, or other biologic use.

DISCUSSION

The CARRA Legacy Registry provided a unique opportunity to study the largest cohort of patients with sJIA reported to date. Demographic features of the CARRA sJIA cohort are similar to previously described smaller cohorts in age at diagnosis, sex, and time to diagnosis[20,21,22]. On the whole, low disease activity was present in the cohort at EV, consistent with other reports[23], likely reflecting the high proportion of patients with sJIA receiving effective treatment at pediatric rheumatology centers, as well as the natural course of disease, in which 40%–50% of patients have a monocyclic or polycyclic rather than a persistent disease course[24,25]. Of note, only 7% had current ACR functional classes III or IV, and median CHAQ was 0.1 (IQR 0.0–0.6) at EV, despite 60.4% reporting ACR class III or IV in the past. Possible explanations for the excellent functional outcomes in this treated sJIA population include early diagnosis and treatment and early initiation of effective biologic therapies. In recently diagnosed patients, physicians more often initiated treatment with IL-1 and IL-6 inhibitors, with nearly one-third of patients taking 1 of these medications. It will be interesting to compare these Legacy Registry data with the new CARRA Registry data to see whether IL-1 and IL-6 inhibitor use has increased even further over time because more data support early aggressive treatment with these agents[9,26].

An intriguing hypothesis suggested by several case series of children with recent onset sJIA is that earlier treatment with effective biologic agents may lead to more rapid suppression of disease activity, favorably altering the disease course and reducing steroid exposure[9,26,27]. Longterm followup studies in children with sJIA in the 1993–2002 decade (before the current biologic era) had shown improvements in functional outcomes[23,24,28,29,30] and mortality compared with studies in earlier decades[31,32,33,34]. Even further improvements in outcomes in the current biologic era have been demonstrated in more recent studies[5,6].

The CARRA Legacy Registry data confirms dramatic recent and rapid changes in the treatment of sJIA. The move away from DMARD and TNF-α inhibitor therapies likely reflects a combination of factors: lack of efficacy of these agents[35,36], demonstrated efficacy of IL-1[6,7,9,10,13] and IL-6 inhibitors[5,37] and their approval by the FDA for sJIA, and the publication of the ACR treatment recommendations and CARRA CTP for sJIA[14,38,39]. A recent study by Otten, *et al* showed that early introduction of biologics may be associated with reduced steroid use in JIA, including sJIA[27]. In the CARRA Legacy Registry cohort, despite the recent trend toward initiation of more aggressive treatment earlier in the disease course, there was no reduction in the overall number of patients taking GC over the study period. However, data related to GC dosing or side effects were not collected, so it is not known whether GC were tapered at a faster rate or used at lower doses compared with earlier timepoints. Although it is possible that medication trends over time could reflect the prescribing preferences of specific sites that were open to enrollment earlier in the enrollment period, medication data were not analyzed by enrolling site.

In this cohort, African Americans appeared to be the major demographic group associated with a higher burden of disease activity. The reasons for this are unclear. Previous analyses of the CARRA Legacy Registry data looking at all JIA categories also showed that African American patients had higher joint counts and worse PGA[40]. Ringold, *et al* showed a larger percentage of families of African American patients with JIA in the CARRA Legacy Registry reporting an annual income of < $50,000 compared with families of white children, suggesting that income or access to care may be confounding variables[40]. However, there was no difference in medication usage in the African American patients compared with the remainder of the cohort. Whether the difference in disease burden is related to underlying genetic or socioeconomic factors, timely access to care, or an ascertainment bias is unclear and warrants further study.

Interestingly, the data also show that patients with higher disease activity at EV were more likely to have received IL-6 inhibitors and TNF-α inhibitors. TNF-α inhibitors were typically used to treat patients with more refractory disease, especially those with persistent chronic arthritis, prior to the availability of IL-1 inhibitors. IL-6 inhibitors, however, were not widely available during the registry enrollment period (having received regulatory approval in 2011) and were likely given only to patients with refractory disease. MTX use was not associated with increased disease activity, perhaps reflecting its past widespread use.

The CARRA Legacy Registry also includes a subset of children with sJIA who continue to have persistent arthritis,

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despite the availability of extremely effective biologic agents[20]. These children may be a distinct subgroup of sJIA, sometimes referred to as systemic onset, polyarticular course JIA. They are often treated with approaches that resemble those used for polyarticular JIA rather than sJIA, and have often been included in clinical treatment trials for polyarticular course JIA. These children have higher joint counts, worse quality of life, and more functional disability, and represent therapeutic challenges for healthcare providers. This may explain the increased use of IL-6 inhibitors, GC, and non-biologic DMARD in these patients. There is a higher frequency of the persistent arthritis–only phenotype in African American patients, which may be related to other findings of more severe disease in this cohort. Our results also show that this persistent arthritis–only subgroup had a shorter time to diagnosis, perhaps reflecting a more aggressive early disease course and arguing against the possibility that this outcome reflects delayed treatment. In addition, although age at diagnosis was similar to that of other children with sJIA, the persistent arthritis-only subgroup had longer disease duration. This could be consistent with the idea that sJIA evolves into this form over time in some patients, or that the cohort that does not develop this phenotype is no longer seeking care by their pediatric rheumatologist because their disease is inactive. Alternatively, changes in current treatment practice may have an effect on the evolution of this phenotype. Molecular data from a study show a different gene expression pattern associated with arthritis in early sJIA compared with the expression pattern in children with persistent arthritis[41]. Specifically, increased IL-10 in circulating immune cells is associated with high joint count in children with both arthritis and systemic features, whereas the lack of IL-4 in these cells is associated with persistence of arthritis without systemic symptoms[41]. In addition, some patients with sJIA who have polyarticular course (persistent arthritis) have been reported to respond to inhibition of T cell costimulation by ABA[42,43]. These findings suggest a model in which both innate and adaptive immune processes contribute to the pathology in at least this subset of patients with sJIA.

Our study was limited by the convenience sampling used by the CARRA Legacy Registry. Analyzing disease activity states over time using a continuous measure such as the Juvenile Arthritis Disease Activity Score would have been informative, but was not feasible. Laboratory data were not collected systematically, and were therefore not analyzed, limiting our ability to determine inactive disease as defined by the Wallace criteria. Similarly, adverse events were not identified systematically. Additionally, systematic detailed data regarding MAS were not collected, which would be of value when looking at associations with disease severity.

Although fulfillment of the ILAR criteria was required for inclusion in the sJIA cohort, 14.5% of patients who were considered to have sJIA by the enrolling physician did not meet the strict ILAR criteria. Of these patients, 36 did not have the requisite quotidian fever pattern, although they may have had fever attributable to sJIA. Although we excluded those who did not meet the ILAR criteria from our analysis, our results show that the demographic and disease activity features of the 2 cohorts did not differ. In a review of 136 patients with sJIA in a Pennsylvania registry, 51% did not meet the ILAR fever criteria at diagnosis[44] and only 30% fulfilled the ILAR criteria despite being diagnosed with sJIA by the treating physician. The absence of quotidian fever and shorter duration of fever may reflect disease heterogeneity at onset, or the need to initiate treatment prior to the requisite 2-week duration of fever, resulting in the resolution of fever or a change in the fever pattern. Although a much higher percentage of the CARRA Legacy Registry cohort met the ILAR criteria (86%, potentially due to the fact that entry in the registry required this), both studies highlight limitations of the criteria, which were primarily developed to identify clinically homogeneous groups of patients for research rather than for diagnosis. Excluding children diagnosed with sJIA by pediatric rheumatologists (despite not fulfilling the ILAR criteria) may not reflect the full clinical spectrum of disease. The CARRA sJIA CTP have eligibility criteria that represent a modification of the ILAR criteria, recognizing that many patients, especially early in the disease, do not fulfill the full criteria, but still need to be treated[14].

The CARRA Legacy Registry data included medication exposures without doses or start and stop dates, limiting the ability to ascertain sequential medication use. The next iteration of the CARRA Registry, which began enrollment in July 2015, is identifying this information. CARRA Registry-wide adoption of the CARRA sJIA CTP[14] and registry collection of longterm data on the CTP-treated patients will yield information on the comparative effectiveness of the most promising therapies currently available. The CARRA sJIA CTP project will analyze outcomes resulting from the early introduction of biologics, which will help clarify the associations we saw with biologic use and disease severity. Analysis of sJIA data from an international collaboration showed that systemic GC as well as biologic use varied greatly based on country of treatment in the first year of disease[45]. Given practice variations, this is clearly an area in need of additional research.

The analysis of medication use trends over time was potentially confounded by the site of treatment; variability in the timing of when each site was activated to enroll patients and the tendency to enroll existing patients (i.e., with longstanding disease) at the time of site activation could affect trends in medication use. The majority of patients were enrolled in years 1 and 2 (73.4% of cohort), and it is possible that patients enrolled in years 3 and 4 were more likely to be recently diagnosed, which may have affected physician treatment choice. Medication choices may also be affected by regional or site preferences[26]. Given that there were over

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50 sites collecting data during the 4-year enrollment period (an average of 1.7 patients/yr/site), it is not possible to statistically rule out these biases. Future research in this area is needed.

Our analyses of the large sJIA cohort in the CARRA Legacy Registry show that the majority of patients with sJIA in North America are doing well, with low disease activity and excellent function and quality of life, although African American patients appear to face a higher burden of disease. However, one-third of the patients in our cohort with disease duration of > 2 years had persistent arthritis; this subset also had a worse prognosis. Future research should focus on these groups to better understand predictors and factors that might improve outcomes. The results also highlight the changing pattern of medication usage for the disease, most specifically the move toward earlier initiation of biologic agents. The availability of large datasets such as the CARRA Legacy Registry, especially if coupled with biospecimen collection and use of standardized treatment plans, will enable better understanding of predictors of response and outcome, as well as the safety and comparative effectiveness of the growing number of medications available to treat patients with sJIA.

APPENDIX 1.

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