

Health Status of Patients with Juvenile Rheumatoid Arthritis at 1 and 5 Years After Diagnosis

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ABSTRACT. Objective. To describe the health and functional status of children with juvenile rheumatoid arthritis (JRA) diagnosed in the early 1990s.

Methods. Patients were obtained from the Pediatric Rheumatology Disease Registry, a database of patients seen in pediatric rheumatology centers across the United States. Questionnaires designed to be filled out after retrospective chart review were sent to pediatric rheumatologists caring for children diagnosed with JRA between 1992 and 1997.

Results. We studied 703 patients — 376 with pauciarticular onset (pauci), 232 with polyarticular onset (poly), and 95 with systemic onset JRA (systemic). At 1 year after diagnosis, half of the pauci and systemic patients no longer required medication, compared to 78% of the poly patients; 98% of the patients functioned in Steinbrocker classes I and II. Six percent of pauci, 27% of poly, and 11% of systemic patients had limitations in school function. Nearly 1/3 of poly patients already had joint space narrowing on radiograph. By 5 years after diagnosis, all pauci, 88% of poly, and 70% of systemic patients were in Steinbrocker classes I and II; but 6% of pauci, 28% of poly, and 44% of systemic patients had limitations in school function. Nearly 2/3 of poly and systemic patients had joint space narrowing.

Conclusion. In these children treated prior to the era of biologic therapy, at 5 years after onset, > 25% of poly and nearly half of systemic patients had functional limitations that required modifications in their school schedule. Radiographically evident joint space damage was seen within a year of onset in poly patients, and by 5 years 2/3 of poly and systemic patients had damage. (*J Rheumatol* 2003;30:394–400)

Key Indexing Terms:

JUVENILE RHEUMATOID ARTHRITIS
OUTCOME

FUNCTIONAL STATUS
MEDICATIONS

Juvenile rheumatoid arthritis (JRA; also referred to as juvenile idiopathic arthritis, JIA) is the most common of the pediatric rheumatic diseases. The incidence of this condition in the United States is generally accepted to be 13.9 per 100,000 children (95% confidence intervals 9.9, 18.8) and the prevalence 113.4 per 100,000 (95% CI 54.6, 155.1)¹.

The 2000 census gives the population of children < 17 years of age as 72,293,812; therefore, each year, between 7157 and 13,590 children in the US can be expected to develop JRA, and there are between 39,470 and 112,130 children with JRA in the US. Given the potential for severe crippling that exists with this condition, it is imperative that children

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Submitted December 11, 2001; revision accepted August 26, 2002.

with JRA be treated in a manner that will ensure their best possible functional outcome.

Although there are longterm studies of JRA that address functional outcome by clinical subgroup²⁻¹⁶, they differ in diagnostic criteria and study design, making comparisons difficult. Further, it is difficult to interpret the results of these studies in the context of the present-day treatment of JRA, which has changed markedly in the last 10 years. In 1992, methotrexate (MTX) was proven to be safe and effective in the treatment of JRA in a randomized placebo controlled trial¹⁷ and replaced gold as the preferred second-line drug¹⁸. Around the same time, pediatric rheumatologists began utilizing intraarticular corticosteroids on a regular basis for the treatment of JRA, with good results, particularly in children with monoarticular disease^{19,20}. On the other hand, biologics such as etanercept and infliximab were not yet available.

The specific aim of this study was to collect information on the health and functional status of children with JRA who were diagnosed in the US in the early 1990s. Data from both 1 and 5 years after onset were compared. It provides retrospective information about the short term (1 and 5 years after diagnosis) outcome of children diagnosed with JRA in the early 1990s, a decade when the treatment of this condition emphasized the use of MTX and intraarticular corticosteroid injection. This information can be used to compare the medical and functional outcomes of children with JRA treated in the era of biologic therapy.

MATERIALS AND METHODS

Patients. From February 1992 to January 2001, members of the Pediatric Rheumatology Database Research Group submitted data to the Pediatric Rheumatology Disease Registry (PRDR). These data consisted of initial diagnosis and demographic information on new patients diagnosed with rheumatic diseases at each of the participating centers. The data were sent to the coordinating center at James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana, and entered into a relational database (Paradox). Patients were listed by code numbers so that their identity was known only to their personal physicians. By February 2001, when data collection ended, physicians at 51 pediatric rheumatology centers across the US had contributed over 49,000 patients to the registry. The 14 centers that had submitted the largest numbers of patients to the database were invited to participate in this retrospective study. Together, these centers had submitted 1050 patients with an initial diagnosis of JRA to the database during the years 1992–97.

The criteria for patient eligibility for this study were: (1) Diagnosis of JRA using the 1977 American Rheumatism Association (ARA; American College of Rheumatology) criteria²¹. This system classifies patients by onset as pauciarticular (pauci), polyarticular (poly), or systemic. Patients with obvious psoriasis and spondyloarthropathies were excluded from this study. (2) Diagnosis did not change since first seen by physician. (3) Patient entered into the PRDR between the years 1992 and 1997. (4) Patient followed by submitting physician for at least one year after diagnosis.

Physicians at each pediatric rheumatology center were provided with the list of patients they had submitted between the above dates. The physicians filled out a brief questionnaire regarding the disease course, medications, current health, and functional status of each patient.

The measures used for outcome were: (1) disease severity as represented by number of hospitalizations, lack of linear growth, joint space

narrowing on radiograph, and loss of vision; and (2) functional status as measured both globally (Steinbrocker class²²) and by the child's ability to participate in full school activities. The number of hospitalizations included admissions secondary to disease activity and complications and brief stays for infusion of medication. Linear growth was quantified by plotting height on standardized pediatric growth charts. Radiographic imaging was not required for this study so not all patients had radiographs done at the specified time points. The radiographs were read by radiologists at each of the pediatric rheumatology centers — there was no attempt to standardize the readings. The percentage of abnormal radiographs is the number of patients with radiographic evidence of joint space narrowing divided by the number of patients in that disease onset group who had radiographs done.

Because of the retrospective design of this study, functional status was quantified by Steinbrocker class²²: Class I is normal; Class II is functional capacity adequate to conduct normal activities despite handicap or discomfort or limited mobility in one or more joints; Class III is functional capacity adequate to perform few or none of the duties of usual occupation or self-care; Class IV is largely or totally incapacitated, with patient bedridden or confined to a wheelchair, permitting little or no self-care.

To determine level of functioning at school, physicians were asked to put each patient into one of 4 categories, based on their function during the majority of the year: (1) able to attend a full day at school with full participation in physical education (PE), (2) able to attend a full day at school but requires modified PE because of JRA, (3) unable to attend a full day at school secondary to JRA, and (4) requires home teaching because of the JRA.

Physicians were not asked to locate patients who had left their care so that the data included only patients who had been managed continuously by pediatric rheumatologists. The forms were then mailed back to the coordinating center for analysis. Because the patients were not identified in any way during this study and the study consisted only of a review of the chart for available information, the Indiana University Institutional Review Board did not require written consent.

RESULTS

Patients. Fourteen pediatric rheumatology centers submitted 1050 patients with JRA to the registry from 1992 to 1997, and of these, 703 children qualified for the study. The remaining 347 patients were excluded because of a change in diagnosis since their initial visit or inadequate length of followup (< 1 year). There were 376 with pauciarticular onset, and of these, 328 (87%) followed a pauciarticular course; the rest developed polyarticular involvement. Sixty percent were antinuclear antibody (ANA) positive, 2% were positive for rheumatoid factor (RF). Of the 232 with polyarticular onset, 48% were ANA positive and 15% RF positive. There were 95 patients with systemic onset disease; 7% had positive ANA, 1% had RF.

Duration of symptoms prior to referral. In 1959, Ansell and Bywaters showed that patients with JRA referred within one year of symptom onset did better than those referred later². The patients in this study were, for the most part, referred early to pediatric rheumatologists (within 6 months of symptom onset; Table 1). Patients with systemic disease seemed to be referred the earliest of all — 65% within 2 months of symptom onset. This is most likely due to the dramatic fevers and multisystem symptoms exhibited by these patients.

Medications. Table 2 lists the medications used in each

Table 1. Interval between symptom onset and referral to a pediatric rheumatologist for patients with each JRA onset type.

Onset Type	Length of Symptoms, months				
	< 1	1–2	2–6	6–12	> 12
Pauciarticular, %	15	24	29	17	15
Polyarticular, %	7	14	29	19	31
Systemic, %	33	32	14	8	13

group of patients. Patients had received the indicated medications at some point during their treatment. No attempt was made to quantify doses, as they all changed often depending on patients' weight, disease activity, and laboratory results. Almost all patients received nonsteroidal antiinflammatory drugs (NSAID). Intraarticular steroids were used in about one-third of pauci and one-quarter of poly and systemic patients. Oral or parenteral steroids were used in 6% of the pauci, 28% of the poly, and 65% of systemic patients. MTX was used in 11% of pauci (the majority were those who followed a polyarticular course), 62% of poly, and 55% of systemic patients.

Of the 235 patients treated with MTX, 86 (37%) were treated within 6 months of onset of symptoms. Two-thirds were treated orally. Forty-seven percent of patients were treated with doses between 0.3 and 0.6 mg/kg/week (less than the currently recommended starting dose¹⁷), another 47% with doses between 0.6 and 1.0 mg/kg/week, and only 4% received doses of 1 mg/kg/week or more (2% did not specify).

At one year after diagnosis, 50% of the patients with pauciarticular onset and course no longer required medication, similar to the 55% of systemic patients (Table 3). Of those patients who followed a polyarticular course, nearly 80% were still taking medication at one year after diagnosis. At 5 years after onset, the majority of the children who were still being followed by pediatric rheumatologists still required medication regardless of their onset subtype.

Disease severity. Figure 1 compares the disease severity at 1 and 5 years after onset as measured by percentage of patients with hospitalizations, linear growth failure, and with radiographic joint space narrowing.

Hospitalizations. At both 1 and 5 years after disease onset, systemic patients had been hospitalized more often than those of other onset types — 55% by one year.

Growth. Linear growth was regarded as an indirect measure of disease severity. There are multiple causes for growth failure in children with JRA, including uncontrolled disease, poor appetite secondary to illness, and, of course, the use of corticosteroid medication to control disease activity. This study did not attempt to differentiate between children who were treated with corticosteroids and those who were not, as the analysis of daily dose and length of therapy is difficult to calculate accurately. It is assumed, however, that only children with severe disease would receive systemic corticosteroid therapy. Whether the growth failure resulted from uncontrolled disease or from the corticosteroid medication used to treat severe disease, we considered that height < 5th percentile was an indirect indicator of severe disease. Six

Table 2. Percentages of patients in each JRA onset group who received medications during their treatment.

JRA Onset Type	Type of Medication					
	NSAID	IA Steroid	Oral/IV Steroid	HCQ	SSZ	MTX
Pauciarticular	99	33	6	6	6	11
Pauci course	99	29	4	4	4	5
Poly course	99	56	19	19	21	52
Polyarticular	99	24	28	28	10	62
Systemic	99	22	65	10	3	55

NSAID: nonsteroidal antiinflammatory drug, IA: intraarticular, HCQ: hydroxychloroquine, SSZ: sulfasalazine, MTX: methotrexate.

Table 3. Percentage of patients with each JRA onset type still taking medication one and 5 years after diagnosis. All patients in the study were followed at least one year after symptom onset.

Onset and Course	Patients Taking Medication 1 yr After Diagnosis, %	Patients Still Being Followed by Same Pediatric Rheumatologist 5 Years After Diagnosis, %	Patients Still Being Followed 5 Years After Diagnosis Who Are Still Taking Medication
Pauciarticular onset	49	46	61
Pauci course	47	38	59
Poly course	78	8	67
Polyarticular onset	81	68	88
Systemic onset	55	56	60

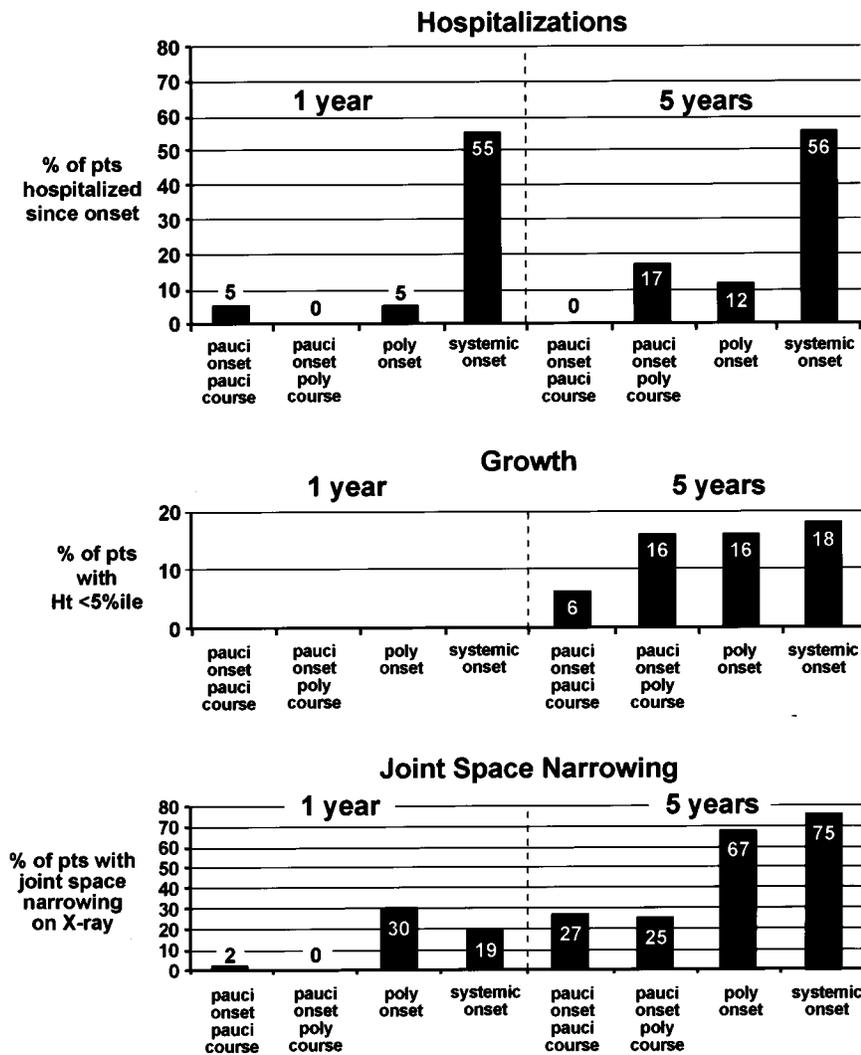


Figure 1. Disease severity in each onset group, showing the percentage of patients in each group who had been hospitalized, the percentage with failure of linear growth, and the percentage with joint space narrowing on plain radiographs. Data are shown for 1 and 5 years after diagnosis.

percent of pauci, 16% of poly, and 18% of systemic patients were 5th percentile or less for height by 5 years after onset. *Radiologic outcome.* The percentage of patients with each onset type who had loss of joint space detected by radiographs is shown in Figure 1. Despite the limitations in standardization of radiographic imaging, it should be noted that 30% of the poly patients who were imaged had radiographic evidence of joint damage by one year after onset. At 5 years after onset, 27% of the pauci patients had abnormalities on radiographic studies as did 67% of poly and 75% of systemic patients.

Visual loss. Respondents were asked whether the patients had uveitis and, if so, whether vision loss had occurred. Of the 376 patients with pauciarticular onset JRA, 48 (13%) had uveitis. Of these 48, 2 (4%) had some loss of vision in only one eye, and 8 (17%) had some loss of vision in both eyes. Of 232 patients with polyarticular onset JRA, 12 had

uveitis (5%) and of those, 2 (17%) had vision loss. Data were available on all 95 of the patients with systemic onset JRA, and none were reported to have uveitis.

Functional status. Figure 2 shows the functional status of this group of children. Global status is indicated by Steinbrocker class, school function is shown separately.

Global function. No patient with pauciarticular onset JRA had significant functional limitations outside of school as measured by Steinbrocker class, even among those followed 5 years after onset. The poly and systemic patients had significantly worse outcomes — at 5 years, 8% of the poly patients were in Steinbrocker class 3 and 4% in class 4, 10% of systemic patients were in class 3 and 20% were in class 4.

School function. Figure 2 depicts the number of patients in each onset group requiring modification in their school programs. At one year after diagnosis, 6% of the pauci

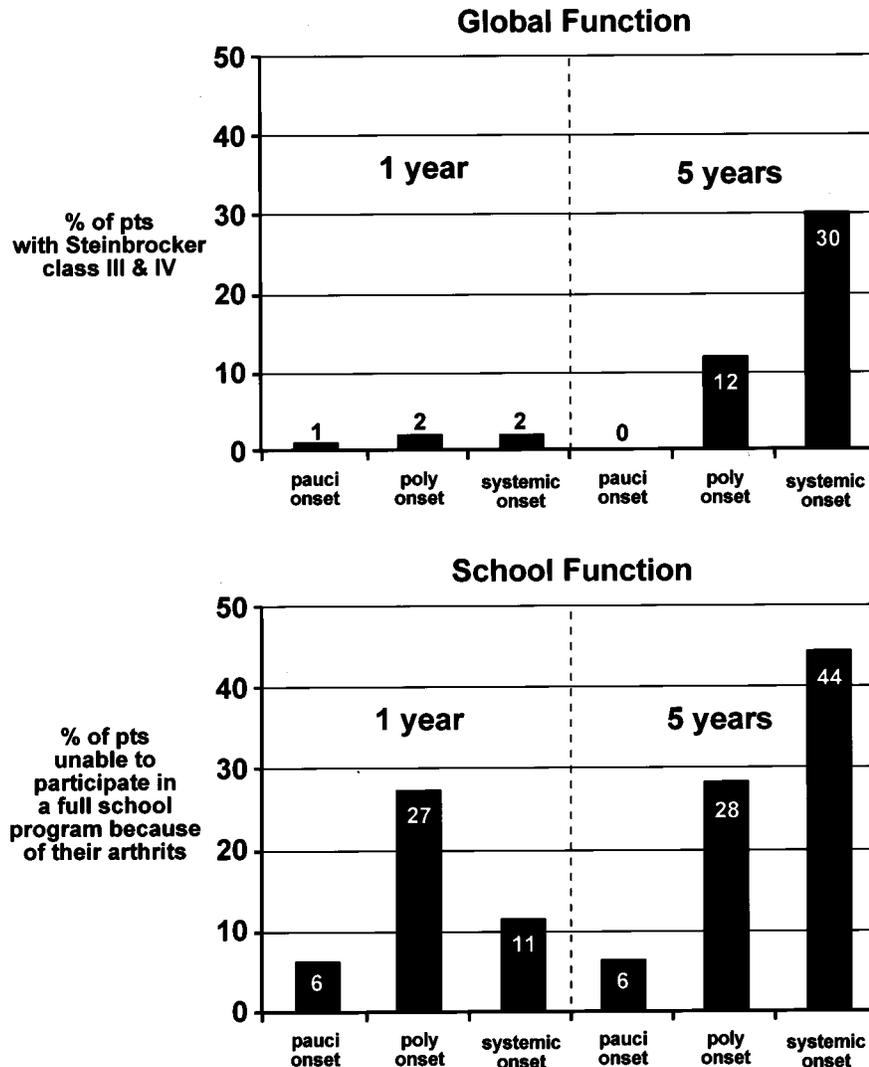


Figure 2. Functional outcome at 1 and 5 years for each onset group: in daily life as depicted by number of patients with severe limitations (Steinbrocker classes III and IV); and in ability to function normally in a school setting. The latter includes children who require modifications in physical education class as well as those who are taking part-time or home schooling because of their arthritis.

patients had limitation in school function compared to 27% of poly and 11% of systemic patients. Most of those children had limitations confined to physical education classes, but 1% of poly and 3% of systemic patients could not tolerate a full day in school because of limitations posed by the arthritis. Of patients still being followed by pediatric rheumatologists 5 years after diagnosis, the proportion of pauci patients with school limitations remained at 6%, while 28% of poly and 44% of systemic patients were limited. Of these, 12% of poly (3 out of 25) and 11% of systemic patients (1 out of 9) required a part-time schedule or home instruction because of their arthritis. These numbers are small, but they represent one patient each at 4 different pediatric rheumatology centers, so the poor outcomes are not the product of skewing from one center.

DISCUSSION

Several factors must be considered when interpreting the results of this study and comparing them with previous reports: the results at one year after onset include all patients who were diagnosed at the submitting centers and followed for at least one year. Since patients had to be followed for more than one year to be included in this study, there was no dropout at the one year time point. The patient population at 5 years after onset, however, consisted only of those who continued to receive care from pediatric rheumatologists, implying an adverse selection bias. (Data from the PRDR suggest that at 5 years after onset, 46% of pauci patients were still being followed, as were 68% of poly and 56% of systemic patients.) Although some patients may have left to seek medical care elsewhere, it is most likely that the

majority of those no longer being cared for by pediatric rheumatologists were discharged from clinic in remission, consistent with our data that nearly half of the pauci and systemic patients were no longer taking medication by one year after diagnosis. The patients reported at 5 years presumably represent the worst cases — those who still have active arthritis 5 years after onset; thus their outcomes do not reflect the outcomes of patients with JRA in general. It is this group of patients who are at highest risk for poor function.

Second, this is a retrospective study using cross sectional data and the data are entirely from physician report; it was impossible to account for all the patients who were no longer being followed and it is not as accurate as following a cohort of patients prospectively. Still, it is the largest cohort of North American patients with JRA ever reported and has the advantage of being able to assess the outcome of a large number of patients diagnosed and treated simultaneously.

Because of the retrospective design of the study, and the fact that the information did not come directly from patient input, we were unable to use the newer functional outcome measures such as the Juvenile Arthritis Functional Assessment Report²³ or the Child Health Assessment Questionnaire (CHAQ)²⁴. The Steinbrocker classes are only rough approximations of function, with a large spectrum of ability within each class, as shown by Gare and Fasth¹⁵. In their study, 69 children were classified as Steinbrocker Class I, but 22 of the 69 scored some degree of disability using the CHAQ disability index. In this study, we were limited to the Steinbrocker classes because the managing physicians could retrospectively classify their patients using these 4 categories.

Since the treatments given to each patient were not standardized, one cannot draw inferences on their effectiveness for patient subgroups. Lastly, since radiographs were not required for the study, they were most likely obtained from the patients with more severe clinical disease. Therefore, the percentage of patients with radiographic changes is higher than it would be in the JRA population in general.

Despite these limitations, several conclusions can still be drawn. First, despite early referral (less than 2 months after symptom onset) and aggressive treatment with corticosteroids, MTX, and joint injections, the outcome for systemic patients was no better than that of patients diagnosed and treated 20 years ago. Half of the patients with systemic disease in this series did poorly, with nearly 50% of those still active at 5 years unable to participate in a full school program and 30% in Steinbrocker classes III and IV. This group was also hospitalized more often than those in the other 2 subgroups. Systemic disease is clearly different from the other forms of JRA.

Most reports on outcome in JRA describe patients 10–20 years or more after onset^{2–16}. These studies place up to 70% (range 0–73) of the patients in Steinbrocker classes III and IV (severe disability). Ansell and Bywaters², Laaksonen³,

and Bywaters⁴ specifically addressed outcome in patients with JRA 5 years after onset. In these studies, 12–39% of patients were in classes III and IV. The functional outcomes we report are better than those in all but one of the previous outcome studies for patients with pauciarticular or polyarticular onset JRA¹⁵ and are equivalent for those with systemic onset disease (Table 4). The excellent results reported by Gare and Fasth¹⁵ may be because they were dealing with a homogeneous population in an area where there was universal access to both health care in general and pediatric subspecialty care, all factors likely to result in optimal outcomes.

An indirect measure of disease severity is the absence of normal linear growth. The numbers of our patients who are < 5th percentile are better than those from the literature^{3,11} and better than the 156 children in the Cincinnati ARAMIS database, where 11% of pauci, 16% of poly, and 50% of systemic patients had height < 5th percentile²⁵. We hypothesize that our improved results reflect the aggressive approach to JRA treatment since MTX and intraarticular corticosteroid injections came into widespread use.

Vision loss is also a form of damage resulting from JRA. Our results are similar to the figures quoted by Petty, *et al*²⁶ and Chalom, *et al*²⁷.

The existence of radiographic evidence of joint space narrowing in 30% of poly patients at one year after diagnosis argues for early diagnosis and aggressive disease modifying treatment. The delay in referring children with polyarticular JRA to pediatric rheumatologists is particularly concerning, given the potential for early joint damage. The reasons for delayed referral are probably multifactorial, and range from lack of awareness on the part of primary care practitioners that arthritis occurs in young children²⁸ to barriers to access imposed by managed care organizations.

To optimize care for children with JRA, primary care providers need to be educated regarding the various clinical presentations of arthritis in children and the importance of prompt referral. Everyone who deals with children with arthritis must be familiar with the structure and function of their local school systems and well versed in the provisions of US federal laws such as the Rehab 504 Act and the IDEA amendment that can help special needs children with difficulties in school settings. This particularly applies to general pediatricians and internist rheumatologists who care for many children with JRA without input from a pediatric rheumatologist. In addition, they must know the current recommendations for ophthalmologic screening for children with arthritis²⁹. Lastly, in view of the high utilization of healthcare and school resources by children with systemic onset disease, it would seem that research efforts that specifically target this subgroup of patients would be both practical and cost effective to society.

A prospective outcome study is currently in progress utilizing this same group of investigators. The next step is to

Table 4. Comparison of JRA outcome studies in the literature and this study. Only studies that divided patients by onset type are listed.

Study	No. of Patients	Length of Followup, yrs	Percentage of Patients in Steinbrocker Classes III and IV		
			Pauci Onset	Poly Onset	Systemic Onset
Calabro 1968 ⁵	100	10	0	12	15
Jeremy 1968 ⁶	46	Mean 18	0	35	
Hill 1976 ⁷	58	Mean 14.5	20	26	73
Calabro 1976 ⁸	100	14–26	0	21	15
Ansell 1976 ⁹	243	18–28	19	28	46
Hanson 1977 ¹⁰	123	5–25	14	20	40
Stoeber 1981 ¹¹	433	10–22	17.5	46	57
Rennebohm 1984 ¹³	250	Mean 15.7	0	17	14
Gare 1995 ¹⁵	124	Mean 7.1	0	5	0
This study, 1 year	251	1	1	2	2
This study, 5 years	69	5	0	12	30

compare the outcome of this cohort of children to the outcome of another cohort diagnosed and treated after 1998, when the tumor necrosis factor inhibitors became available. In the same way that this cohort of children had better outcomes than children from previous decades, it is hoped that future studies will show better outcomes than those seen in our cohort of patients.

ACKNOWLEDGMENT

We thank Karla Jones, RN, CNS, Lenora Barnes, RPT, Ruth Aiken, RN, Christina Elwood, AB, Jaylene Weigel, RN, Susan Hunter, Melissa Belvedere, RN, and Jackee Wuellner for recruiting patients and collecting data.

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