Course of Joint Disease in Patients with Antinuclear Antibody-positive Juvenile Idiopathic Arthritis

ENRICO FELICI, CRISTINA NOVARINI, SILVIA MAGNI-MANZONI, ANGELA PISTORIO, ALESSANDRA MAGNANI, ELENA BOZZOLA, ANTONELLA BUONCOMPAGNI, ALBERTO MARTINI, and ANGELO RAVELLI

ABSTRACT. ***Objective***. To describe the patterns and time course of arthritis in patients with antinuclear antibody (ANA)-positive juvenile idiopathic arthritis (JIA).

Methods. We identified patients followed during a 16-year period who had JIA by ILAR criteria, were ANA-positive (i.e., had ≥ 2 positive ANA test results at titer ≥ 1:160), and had a disease duration ≥ 2 years. Demographic and clinical features, including ILAR category and cumulative number and type of joints affected over time, were recorded.

Results. A total of 195 patients were studied. The ILAR category was oligoarthritis in 159 patients and rheumatoid factor-negative polyarthritis in 36 patients. The cumulative rate of polyarticular extension in patients with oligoarticular onset was 26%, 38%, 45%, 49%, and 51% at 1, 2, 3, 4, and 5 years, respectively. At disease onset, most patients had monoarthritis and 95% had ≤ 4 joints affected. The knee was the most frequently involved of all joints, followed by the ankle and proximal interphalangeal joints. Among patients with oligoarticular onset, the presence of ankle (in case of monoarticular disease) and/or wrist involvement in the first 6 months was more common in those who progressed to polyarthritis.

Conclusion. The majority of our ANA-positive patients, including most of those who later developed polyarthritis, had monoarthritis at disease onset. Among patients with oligoarticular onset, polyarticular extension occurred in around 50% of cases within the first 3–4 years after disease onset, and tended to be less likely thereafter. The early occurrence of ankle and/or wrist disease may indicate a higher likelihood of arthritis progression. (J Rheumatol 2005;32:1805–10)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS
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POLYARTHRITIS

The presence of circulating antinuclear antibodies (ANA) identifies a subgroup of patients with juvenile idiopathic arthritis (JIA) who share some distinctive clinical features, which include early onset (usually before 6 years of age), female predilection, predominance of asymmetric arthritis, and high risk for developing chronic anterior uveitis[1,2]. However, the course of joint involvement in this patient subset is known to be variable.

In the current International League of Associations for Rheumatology (ILAR) classification for JIA[3], ANA-positive patients may fall in the oligoarthritis or rheumatoid factor (RF)-negative polyarthritis categories, depending on the number of joints affected in the first 6 months of disease (1 to 4 or 5 or more, respectively). Patients with oligoarticular onset are further classified in a "persistent oligoarthritis" category if the arthritis remains restricted to 1–4 joints throughout the disease course, or in an "extended oligoarthritis" category if 5 or more joints become affected after the first 6 months of disease. We previously found that, compared with ANA-positive patients with oligoarthritis or polyarthritis, ANA-negative patients with the same disease categories were older at disease presentation and had a lower frequency of iridocyclitis[2]. Further, compared with ANA-positive patients with polyarthritis, ANA-negative patients with polyarticular disease had a higher frequency of symmetric arthritis, a greater cumulative number of joints

From the Dipartimento di Pediatria, Università di Genova, Unità Operativa Pediatria II, Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova; Dipartimento di Pediatria, Università di Pavia, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia; and Servizio di Epidemiologia e Biostatistica, Direzione Scientifica, Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini, Genova, Italy.

E. Felici, MD, Resident in Pediatrics; C. Novarini, MD, Resident in Pediatrics; A. Magnani, MD, Resident in Pediatrics; A. Buoncompagni, MD, Dirigente Medico I livello; A. Martini, MD, Professor of Pediatrics; A. Ravelli, MD, Dirigente Medico I livello, Dipartimento di Pediatria, Università di Genova, Unità Operativa Pediatria II, Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini; S. Magni-Manzoni, MD, Dirigente Medico I livello; E. Bozzola, MD, Resident in Pediatrics, Dipartimento di Pediatria, Università di Pavia, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo; A. Pistorio, MD, PhD, Dirigente Medico I livello, Servizio di Epidemiologia e Biostatistica, Direzione Scientifica, Istituto di Ricovero e Cura a Carattere Scientifico G. Gaslini.

Address reprint requests to Dr. A. Ravelli, Pediatria II, Istituto G. Gaslini, Largo G. Gaslini 5, 16147 Genova, Italy.
E-mail: angeloravelli@ospedale-gaslini.ge.it

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affected over time, and a different pattern of joint disease, with greater frequency of shoulder and hip involvement[2].

We investigated the patterns and time course of joint involvement in a cohort of patients with ANA-positive JIA.

MATERIALS AND METHODS

Patient selection. This was a retrospective cohort study of patients followed at the pediatric departments of the universities of Pavia and Genova, Italy, between January 1987 and December 2002. Most were part of a previous analysis that compared the clinical features of ANA-positive and ANA-negative JIA patients[2]. Inclusion criteria were the following: (1) a diagnosis based on the ILAR criteria for JIA[3] (i.e., arthritis of unknown etiology persisting for at least 6 weeks with onset before the 16th birthday); (2) a positive ANA test, defined as at least 2 positive results of ANA determination on indirect immunofluorescence on HEp-2 cells at a titer ≥ 1:160 made at least 3 months apart[2]; and (3) a disease duration from disease presentation to the last followup visit of at least 2 years.

Patients were excluded if they met the ILAR criteria for systemic arthritis, RF-positive polyarthritis, enthesitis-related arthritis, or psoriatic arthritis. Patients with a positive family history of psoriasis (which is an exclusion criterion from the oligoarthritis category in the ILAR classification) were not excluded, because we previously found close similarities in the clinical features and disease course among patients with oligoarthritis who had a positive family history and those who did not[2,4].

Clinical assessments. Patients were identified through existing databases and/or clinic files. The medical charts were reviewed for the following information: sex, age at disease onset, ILAR category, disease duration from onset to the last followup visit, and cumulative number and type of joints involved at onset and in the first 6, 12, 24, 36, 48, and 60 months after disease onset. Date of disease onset was defined as the date when the first symptoms of arthritis were noted, obtained by history as recorded in the charts. Gathering data on joint involvement at specific time intervals was easier because we routinely perform and record on standardized sheets a detailed joint assessment of each patient at each clinical evaluation. At each visit, a total of 67 joints (those that are included in the normal clinical evaluation) were examined for the presence of swelling, pain on motion/tenderness, and limited range of motion. For purposes of analysis, the ankle and subtalar joint were considered as a single unit. All joint assessments were performed by the same 2 investigators, who followed the same methodology throughout the whole study period.

Definition of joint patterns. At each study timepoint, 4 different patterns of arthritis were identified based on the cumulative number of affected joints: monoarthritis (involvement of 1 joint); oligoarthritis (involvement of 1–4 joints); polyarthritis (involvement of 5–10 joints); and severe polyarthritis (involvement of ≥ 11 joints).

Statistics. Comparison of the frequency of polyarticular extension at 2 and 5 years between patients who had 1 or 2–4 joints involved in the first 6 months was assessed using the chi-square test. The cumulative rate of polyarticular extension among patients with oligoarticular onset was calculated by the Nelson-Aalen method[5].

RESULTS

A total of 195 patients, 163 girls and 32 boys, were included in the study. Age at disease presentation ranged from 0.9 to 14.4 years (mean 3.6 yrs) and disease duration from presentation to the last followup visit from 2 to 24.6 years (mean 6.9 yrs). One hundred ninety-five patients had a followup of at least 2 years and 126 patient had followup of at least 5 years. Of the 69 patients who did not reach the 5-year followup, 55 were still followed at the time of the study but had a disease duration < 5 years, and 14 were lost to followup; in the latter group, only 1 patient had inactive disease at the last followup visit. The ILAR category was oligoarthritis in 159 patients and RF-negative polyarthritis in 36 patients. The cumulative rate of polyarticular extension in the 159 patients with oligoarticular onset was 26% at 1 year, 38% at 2 years, 45% at 3 years, 49% at 4 years, and 51% at 5 years (Figure 1).

Figure 2 shows the frequency of the 4 patterns of joint disease at each study timepoint. At disease presentation, about three-quarters of patients had involvement of a single joint and 95% had ≤ 4 joints affected; no patient presented with simultaneous involvement of ≥ 11 joints. At 6 months after disease presentation, the frequency of monoarthritis was diminished to one-third and that of oligoarthritis was doubled; one-fifth of the patients had polyarthritis, which was severe in only 4% of them. The frequency of monoarthritis decreased progressively from the 6-month to the 3-year assessment and remained stable at 12% afterward. A similar, although less pronounced, decline was seen for oligoarthritis, which was still detectable in 36% of the patients at 5 years. In contrast, the frequency of polyarthritis increased progressively after the 6th month, but reached a plateau at around 40% after the 3rd year. The severe polyarticular pattern was uncommon at all timepoints and remained constant at 12% after the 3rd year.

The frequency of involvement of specific joints in the first 6 months of disease by pattern of arthritis is presented in Figure 3. As expected, the knee was the most commonly affected joint across the 4 patterns. In patients with monoarthritis, the knee was involved 4 times more frequently than the ankle. In all patterns, the proximal interphalangeal joint ranked third in order of frequency after the knee and ankle. Involvement of wrist, elbow, and metacarpophalangeal joints was much more common in patients with polyarthritis than in those with monoarthritis or oligoarthritis. Cervical spine and metatarsophalangeal joints were affected with noticeable frequency only in patients with severe polyarthritis, whereas hip disease was distinctly uncommon in all 4 categories.

Tables 1 and 2 summarize the changes in the joint pattern from the 6-month to the 2-year assessment and from the 2 to the 5-year assessment, respectively. In both time intervals, the frequency of persistence in the initial pattern or progression to the more expanded patterns was remarkably similar among patients with monoarticular and oligoarticular onset. Both these cohorts progressed very rarely to severe polyarthritis (1.5% and 3.2% of cases, respectively, at 2 years and 0% and 3.7% of cases at 5 years). This extension was more common in the polyarthritis subgroup, although only 22% and 12.5% of these patients developed the severe polyarthritis pattern at 2 and 5 years, respectively. Among patients who had oligoarthritis in the first 6 months of disease, the frequency of polyarticular extension at 2 and 5 years was more common in those who had involvement of

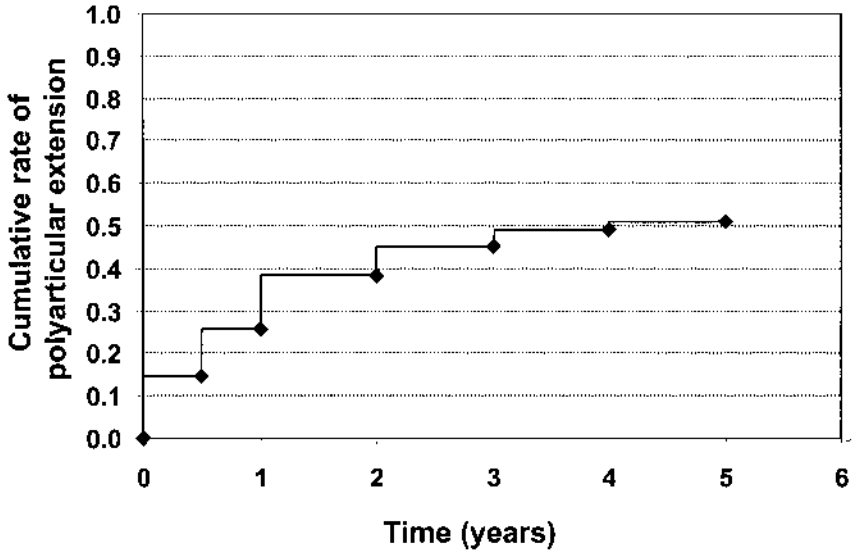

Figure 1. Nelson-Aalen curve of the cumulative rate of extension to polyarthritis over time in patients with oligoarticular onset disease.

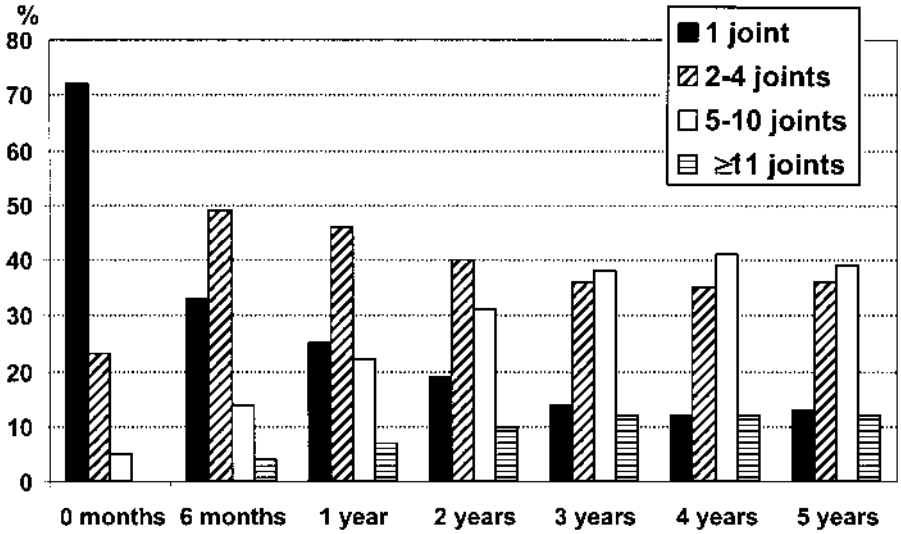

Figure 2. Frequency of the 4 different patterns of joint disease at each study timepoint.

2–4 joints than in those who had monoarthritis ($p < 0.0001$ at 2 years and $p = 0.05$ at 5 years).

Comparison of the type of joints with change in joint pattern from the 6-month to the final assessment in patients who were followed for 5 years is presented in Table 3. Notably, the frequency of ankle involvement was much more common in patients with monoarthritis who progressed to polyarthritis than in those who remained monoarticular or experienced a limited spreading to oligoarthritis. Further, among patients with monoarthritis or oligoarthritis, wrist involvement was seen only in those who progressed to polyarthritis or severe polyarthritis.

DISCUSSION

We investigated the patterns and time course of arthritis in a cohort of patients with ANA-positive JIA. We chose this patient group because it has been shown to share homogeneous clinical features (early onset, marked female predilection, asymmetric arthritis, and high risk of chronic iridocyclitis)[2], is known to have a variable articular course, and represents the majority of the JIA population in our country.

Knowledge of the course of joint disease and, in particular, of the risk of arthritis spreading is needed in order to provide prognostic information and to present appropriate treatment options to JIA patients and their families. Studies

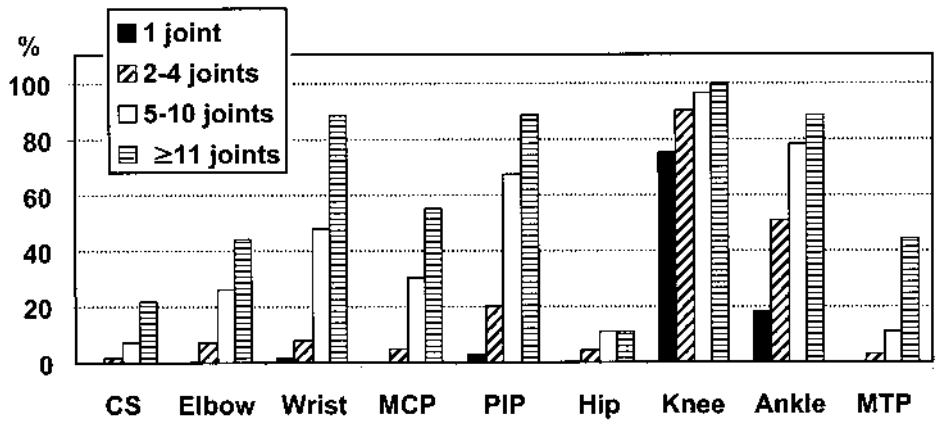

Figure 3. Frequency of type of joints involved in the first 6 months of disease by pattern of joint disease. CS: cervical spine; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; MTP: metatarsophalangeal joints.

Table 1. Changes in the pattern of joint disease from 6 months to 2 years.

Joint Pattern at 6 mo	No. Patients (%) (N = 195)	Joint Pattern at 2 yrs	No. Patients (%) (N = 195)
1	65 (33.3)	1	38 (58.4)
		2–4	21 (32.4)
		5–10	5 (7.7)
		≥ 11	1 (1.5)
2–4	94 (48.2)	2–4	56 (59.6)
		5–10	35 (37.2)
		≥ 11	3 (3.2)
5–10	27 (13.9)	5–10	21 (77.8)
		≥ 11	6 (22.2)
≥ 11	9 (4.6)	≥ 11	9 (100)

Table 2. Changes in the pattern of joint disease from 2 to 5 years.

Joint Pattern at 2 yrs	No. Patients (%) (N = 126)	Joint Pattern at 5 yrs	No. Patients (%) (N = 126)
1	24 (19.0)	1	16 (66.6)
		2–4	6 (25.1)
		5–10	2 (8.3)
		≥ 11	0 (0)
2–4	54 (42.8)	2–4	39 (72.2)
		5–10	13 (24.1)
		≥ 11	2 (3.7)
5–10	40 (31.7)	5–10	35 (87.5)
		≥ 11	5 (12.5)
≥ 11	8 (6.3)	≥ 11	8 (100)

have indicated that patients with oligoarticular onset whose disease follows an extended (i.e., polyarticular) course are likely to have a worse prognosis and, in particular, to carry a high risk of joint destruction[6-8]. Since articular damage has been found to develop early in the disease course, it has been suggested that oligoarticular patients with a high probability of polyarticular extension who are resistant to nonsteroidal antiinflammatory drugs and corticosteroid joint injections deserve an early aggressive therapeutic approach with second-line drugs, such as methotrexate[9].

The time course of joint disease in oligoarticular-onset JIA has seldom been investigated. Further, no study has restricted the analysis to ANA-positive patients, making comparison with our study difficult. In a group of 207 patients, 75% of whom were ANA-positive, Guillaume, *et al*[9] found that polyarticular involvement occurred preferentially within the first 2 years of the disease course. The risk of extension was estimated at 30%, 40%, and 50% after 2, 4, and 6 years of disease duration, respectively, and the risk of severe polyarticular involvement (≥ 10 joints) at 8%, 13%, and 18% after 2, 4, and 6 years, respectively. A global frequency of extension to polyarthritis and to arthritis in ≥ 10 joints of 39.5% and 17.6%, respectively, was reported by Al-Matar, *et al*[10] in 205 patients with oligoarticular-onset JIA with a median disease duration of 10.8 years, 61% of whom were ANA-positive. Oen, *et al*[11] found that 20% of 198 of patients with oligoarticular onset disease, whose ANA status was not specified, developed extended disease, with the median time to extension being 3.9 years. Extension occurred in only 21% of cases within 2 years after onset. The frequency of polyarticular extension in our patients with oligoarticular onset is similar to that observed by Guillaume, *et al*[9] and Al-Matar, *et al*[10] and higher than that reported by Oen, *et al*[11]. We found, among all joint patterns, a tendency for the accumulation of affected joints over time to become stable at around 3–4 years after disease presentation. This finding suggests that if extension of arthritis occurs, it occurs most often in the first 4 years after onset.

In our cohort, as many as 72% of patients, including most of those who developed a polyarticular disease course, presented with arthritis in a single joint. A similar percentage of monoarticular presentation (78%) was reported by Guillaume, *et al*[9]. Further, nearly all patients (95%) had ≤ 4 joints affected at onset, supporting the notion that the arthritis in ANA-positive JIA patients is intrinsically asymmet-

Table 3. Type of joints affected in the first 6 months by change of joint pattern from 6 months to 5 years.

Joint Pattern, 6 mo → 5 yrs	No. Patients (N = 126)	CS, %	Elbow, %	Wrist, %	MCP, %	PIP, %	Hip, %	Knee, %	Ankle, %	MTP, %
1 →1	16					6		75	19	
1→2–4	13							84	15	
1→5–10	11					9		45	45	
1→≥ 11	2			50				50		
2–4→2–4	32		6			16		97	50	6
2–4→5–10	27			18	11	33	7	85	48	4
2–4→≥ 11	6		33			33	17	67	50	
5–10→5–10	12	17	25	50	83	67		17	75	8
5–10→≥ 11	4			75	50	100		75	75	25
≥ 11→≥ 11	3		66	67	33	67		100	100	67

CS: cervical spine, MCP: metacarpophalangeal joints, PIP: proximal interphalangeal joints, MTP: metatarsophalangeal joints.

ric[1]. The severe polyarticular pattern was detected in only 12% of the patients at all study timepoints. The rate of extension to severe polyarthritis was very low during the whole disease course among patients who started with monoarthritis or oligoarthritis.

In the first 6 months, the knee, ankle, and proximal interphalangeal joints were the articular sites most frequently affected in patients with monoarthritis and oligoarthritis. The observed rates are similar to those reported by other investigators[10,12]. The elbow, wrist, and metacarpophalangeal joints were involved with substantial frequency only in patients with polyarthritis or severe polyarthritis. Early involvement of the hip joint was uncommon in all subgroups; however, at 2 and 5 years the hip joint was affected in only 1 patient with persistent oligoarthritis and in 13% to 20% of patients with polyarthritis (data not shown).

A few studies have examined predictive factors associated with poor outcome specifically for oligoarticular JIA. Guillaume, *et al* found that the presence of more than 1 affected joint, the involvement of at least 1 upper limb joint, or a high erythrocyte sedimentation rate (ESR) at onset (particularly when > 100 mm/h) independently predicted a polyarticular disease course[9]. The early presence of symmetric disease, ankle and/or wrist involvement, and elevated ESR were significantly predictive of a polyarticular extension in the study by Al-Matar, *et al*[10]. Our analysis was essentially descriptive and was not aimed at identifying early prognostic factors. However, we found that among patients with monoarthritis, early ankle involvement was much more common in those who progressed to polyarthritis, and that among patients with monoarthritis or oligoarthritis early wrist disease was detectable only in those who experienced a polyarticular extension. These findings, together with those of Al-Matar, *et al*, suggest that in patients with oligoarticular-onset JIA the presence of ankle (in case of monoarticular disease) and/or wrist involvement in the first months of disease indicate a likelihood of disease progression.

We acknowledge the limitations imposed by the retrospective design of our study. In some patients the topography of the affected joints at earlier timepoints was determined from parent-reported histories recorded in clinical charts, leading to a potentially inaccurate estimation of the distribution of arthritis. Although the cohort was represented by every consecutive patient seen at a large tertiary care center, the study was referral based, and thus we cannot exclude a selection of severe cases. Although patients with early remission were not excluded by the study design, those who entered remission within 2 years were more likely to have been lost to followup, and not including this patient population may have introduced a further bias. We also recognize that the lack of exclusion of patients with a positive family history of psoriasis represents a diversion from the current ILAR criteria. In the absence of an established threshold to define ANA positivity, we chose a cutoff of ≥ 1:160, and were able to confirm this level of ANA positivity in all patients. It remains to be determined where patients with lower-titer ANA (e.g., 1:40 or 1:80) would fit. During the time period in which these patients were enlisted there were many therapeutic advances, including the introduction of methotrexate and increasing use of intraarticular injections with triamcinolone hexacetonide. It is not known how these medications influence the prognosis of spreading of arthritis. This potential confounding factor could not be addressed. The main strengths of our study lie in the clinical homogeneity of the patient population and in the close time sequence and comprehensiveness of joint assessments.

We found that about 50% of our patients with ANA-positive, oligoarticular-onset JIA experienced a polyarticular extension of their arthritis, which occurred most commonly in the first 3–4 years after disease onset. The majority of patients, including most of those who later developed polyarthritis, had arthritis in a single joint at disease presentation. Although roughly half the whole patient cohort had polyarthritis at 5 years, the presence of a severe polyarticular pattern (i.e., involvement of ≥ 11 joints) was seen in only 12% of cases. In patients with oligoarticular onset, the early

presence of ankle (in cases of monoarticular disease) and/or wrist involvement may indicate a higher probability of arthritis progression. Further studies are needed to compare the longterm outcome of the different joint patterns, particularly in terms of the likelihood of achieving clinical remission[12].

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