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Remission in Juvenile Chronic Arthritis: A Cohort Study of 683 Consecutive Cases with a Mean 10 Year Followup

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ABSTRACT. ***Objective.*** As continuity of care in our institution allows longterm followup studies, we reviewed the files of all consecutive patients with juvenile chronic (idiopathic) arthritis (JCA) followed since 1970 to establish the frequency of remission.

Methods. Charts of all patients with JCA were reviewed. Relevant variables were entered into a customized database. The presence of remission (lack of signs of disease activity in the absence of antirheumatic therapy for at least 6 mo) during the disease course and at the last visit was assessed.

Results. The cohort included 683 patients, 463 females and 220 males. According to the disease onset, 420 had oligoarticular, 108 polyarticular (23 rheumatoid factor positive), and 88 systemic disease; 67 had a juvenile spondyloarthropathy (SpA). For all 4 categories the mean followup period was about 10 years. At the last visit 224 cases were in remission (32.8%). Remission rate was scarcely influenced by age at disease onset, but differed in the different disease categories. Of the total group of 683 patients, 153 (22.4%) were lost to followup (no control for at least 2 years). For all 4 categories the remission rate at the last visit was higher in patients who had been lost to followup: 42.3% versus 29.0% for systemic onset JCA, 20.8% versus 16.5% for polyarticular onset JCA, 44.7% versus 33.6% for pauciarticular onset JCA, and 66.7% versus 26.8% for juvenile SpA. The probability of attaining remission decreased in proportion to delay in entering the tertiary care center (from 35.7% to 22.8%). The rate of remission reached its peak after 5–10 years of followup, after which the trend reversed.

Conclusion. Childhood arthritis achieved remission in only about one-third of our cases, with differences among disease categories based on the diagnosis. (J Rheumatol 2003;30:579–84)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS JUVENILE CHRONIC ARTHRITIS
ARTHRITIS REMISSION PROGNOSIS OUTCOME

Juvenile chronic (idiopathic) arthritis (JCA) is the most common pediatric rheumatic disease in developed countries, and can potentially lead to severe disability; it is now generally accepted that this is not a single disease but rather a heterogeneous group of different conditions. The natural history of these conditions is not fully known: remission has been reported in different series as varying from 15% to 70%[1]. Many reasons underly these discrepancies, one being the difficulty of performing longterm studies, because many patients are often lost to followup when they reach young adulthood. Moreover, heterogeneity in patient selection, disease classification, criteria for remission assessment and definition, and type of facility make comparisons between studies very difficult.

In this regard, the Gaetano Pini Institute in Milan has the advantage of being a referral center for both children and adults with arthritis; therefore patients can be followed in the same institution even after they reach adulthood, so that there is a relatively low rate of patients lost to followup. Moreover, data collection over time is uniform. We evaluated the remission rate in our cohort of patients with JCA, and correlated it with different aspects such as clinical diagnosis, age at disease onset, duration of followup, and delay in referral to our center.

MATERIALS AND METHODS

All patients diagnosed with JCA and attending our center from 1970 to 1998 were eligible; to be enrolled in the study, a minimum followup of one year was required. Patients are sent by their referring doctors or from other hospitals, without restrictions and at no charge for the patient since the Italian health system is public. During the followup period no significant changes in the pattern of referral were observed. Patients were classified into 4 categories according to the European League Against Rheumatism

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(EULAR)[2] and European Spondylarthropathy Study Group (ESSG)[3] criteria: systemic onset JCA, polyarticular onset JCA, oligoarticular onset JCA, and juvenile spondyloarthropathies (SpA).

All charts were retrospectively reviewed by a single physician and a customized data collection sheet was created, which included relevant variables such as demographic data, laboratory tests, and clinical status at each clinic visit. For this study, disease was considered active (active joints and abnormal laboratory tests during treatment), inactive (no active joints, but still undergoing treatment), or in remission. Remission was defined as no signs of disease activity (active joints and/or positive laboratory tests) in the absence of antirheumatic therapy, including local corticosteroid injection and nonsteroidal antiiflammatory drugs (NSAID), for at least 6 months (12 months for oligoarthritis if a joint had been previously injected with long-acting corticosteroids). Remission was considered both at the last recorded visit and during the whole course of followup.

Differences in demographic and clinical data between the groups were assessed by Student t test. Differences in frequencies were tested by chi-square test or Fisher's exact test, where appropriate. Chi-square test (1 degree of freedom) was used to evaluate trends. All reported p values were 2 sided. All calculations were performed using Instat 2 software.

RESULTS

Clinical characteristics of the whole cohort are shown in Table 1. Regarding the different disease categories, the majority of our patients (n = 420) had disease of oligoarticular onset; of those, 104 (24.8%) were male and 316 (75.2%) were female. Median age at disease onset was 3.3 years (range 0.5–15.7), median disease duration before referral was 0.6 year (range 0–17.1), and median disease duration at last visit was 8.1 years (range 0.6–33.4). In this group, 320 patients (77.1%) had a persistent oligoarticular course, while 100 (23.8%) had an extended (polyarticular) course. One hundred eight patients had a polyarticular onset (15.8%); of those, 32 (29.6%) were male and 76 (70.4%) were female. Median age at disease onset was 7 years (range 0.7–15.9), median disease duration before referral was 1 year (range 0–30), and median disease duration at last visit was 9.9 years (range 0.9–36). In this group, 23 patients (21.3%) were positive for rheumatoid factor (RF), 85 (78.7%) were RF negative. Eighty-eight patients had a systemic onset JCA (12.8%); of those, 41 (46.6%) were male and 47 (53.4%) were female. Median age at disease onset was 6 years (range 0.7–15.9), median disease duration before referral was 1.5 years (range 0–26.3), and median disease duration at last visit was 10.9 years (range 0.8–36.6). Sixty-seven patients were classified in the juvenile SpA group (9.8%); of those, 43 (64.2%) were male and 24 (35.8%) were female. Median age at disease onset was 10.8 years (range 1.1–15.9), median disease duration before referral was 1 year (range 0–15), and median disease duration at last visit was 8.7 years (range 0.8–28.3). In this group, 23 patients had psoriatic arthritis, 10 had ankylosing spondylitis, 3 had arthritis associated with inflammatory bowel disease, and 31 had undifferentiated SpA.

Differences in sex distribution and age at disease onset reflected the well known features of the different clinical subsets; however, the mean duration of followup was similar (about 10 years, range 9.3–11.1) for the 4 categories. Considering the whole cohort, the disease status at the last visit was remission in 224 cases (32.8%), active disease in 287 (42%), and inactive in 172 (25.2%). Figure 1 shows remission rates at the last visit in the 4 groups of patients according to clinical diagnosis. As shown, the lowest percentage of remission (17.6%) is represented in the polyarticular onset group, which was the only one statistically different from the others with regard to remission rate at the last visit. In the oligoarticular group there were about one-quarter (100/420) of patients who had a polyarticular course; these behaved similarly, if not worse, than the group with polyarticular onset, with a remission rate at the last visit of 13%, in contrast to 43.4% in the other 320 patients whose disease remained oligoarticular throughout the followup period.

Neither sex nor age at onset (data not shown) seemed to influence remission in our patients: indeed, remission rates were not significantly different splitting the cohort in 3 groups according to age at disease onset (0–5, 5–10, and 10–16 years). Also, considering age at onset in the 4 categories, no significant trend was observed in percentage remission rates.

We also considered the percentage remission rates at the last visit according to the duration of followup. Percentages in the whole cohort are shown in Figure 2: the maximal remission rate was achieved in patients with a followup of 5–10 years, and after that the percentage slowly declines. We also performed the same analysis in the different disease groups; of note, no clear trend toward an increasing remission rate with time was observed in any group. In particular, none of the 8 patients with juvenile SpA followed for more than 20 years was in remission at the last visit.

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Table 1. Characteristics of the whole cohort (n = 683), male 220 (32.2%), female 463 (67.8%).

	Mean	SD	Median	Range
Age at disease onset, yrs	6.1	± 4.3	3.5	0.5–15.9
Age at first visit at referral center, yrs	8.5	± 5.5	7.6	0.7–33
Disease duration before referral, yrs	2.4	± 3.9	0.8	0–30
Observation period,yrs	7.6	± 5.9	6.2	0.5–35
Age at last visit, yrs	16.1	± 7.6	15.5	2.2–41.3
Disease duration at last visit (followup), yrs	10.2	± 7.15	8.8	0.6–36.6

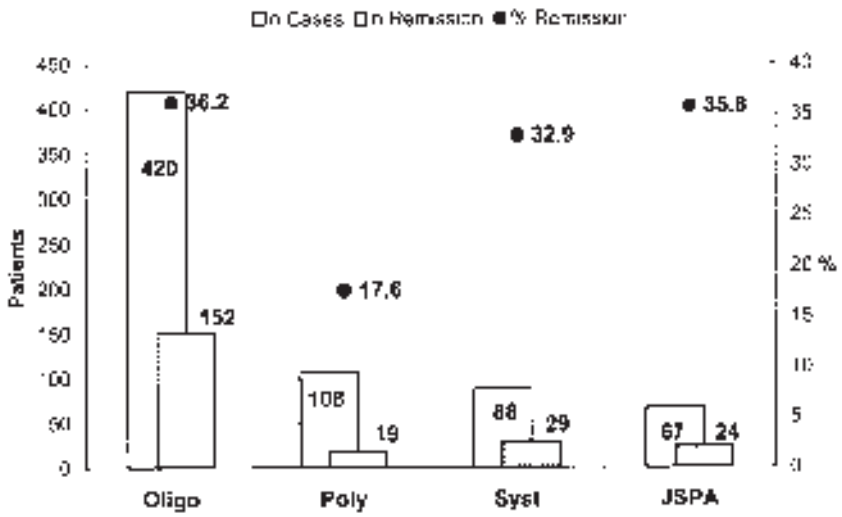

Figure 1. Percentage remission rates at the last visit according to clinical diagnosis for each category. White columns are number of cases, shaded columns are number of cases in remission at the last visit (left scale). ●: percentage of remission for each category (right scale). Remission rate of the Poly group was significantly lower than that of the other groups: comparison Oligo-Poly p = 0.0004; Syst-Poly p = 0.02; juvenile SpA-Poly p = 0.011; no significant differences between the other categories (chi-square test).

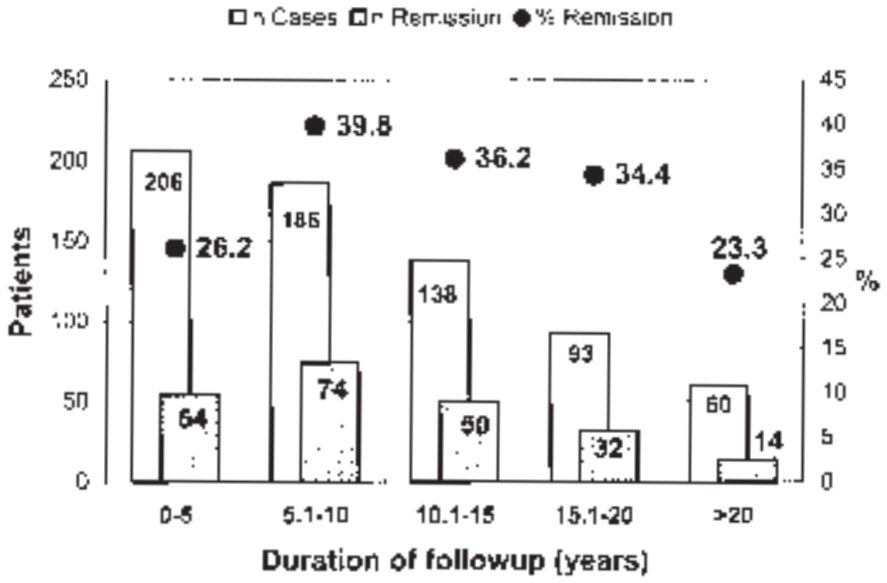

Figure 2. Percentage remission rate at the last visit according to duration of followup for the whole cohort. Details as in Figure 1.

visit, but also during the disease course, we observed that 398 (58.3%) patients never achieved remission, while 285 (41.7%) patients had at least a period of remission, of variable duration (mean 53.7 ± 38.3 months, range 6–207). Considering the different disease categories, three-quarters of the patients with polyarticular onset disease never achieved a remission; this percentage rises in RF positive patients, none of whom ever achieved a remission during their disease course. Figure 3 shows remission during the disease course in the 4 clinical categories. As can be seen, a significant number of patients with systemic onset disease also never had a remission. By contrast, the 2 groups (never remission and at least one remission) were similar in patients with oligoarticular JCA (223 vs 197 patients) and juvenile SpA (35 vs 32 patients). Percentages of patients who never achieved remission (neither during disease course nor at last visit) were 53.1% for oligoarticular JCA, 75.9% for polyarticular JCA (100% for RF positive

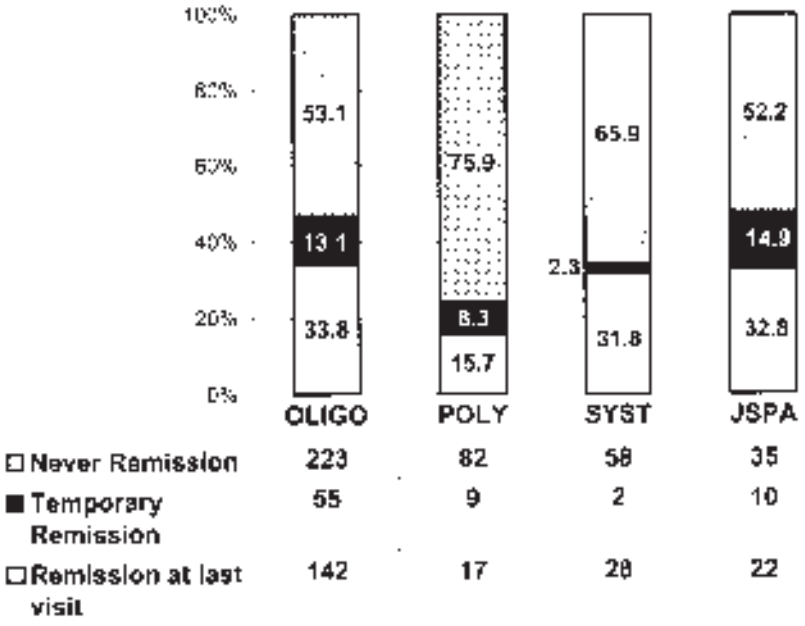

Figure 3. Percentages of patients who never had a remission, who had a temporary remission but were not in remission at last visit, and who were in remission at last visit, for each disease category. Number of cases given at the bottom.

patients), 65.9% for systemic JCA, and 52.2% for juvenile SpA. There was a higher percentage of patients who never achieved remission in the group who were seen > 5 years after disease onset (69%) as compared to those seen within 5 years (56%).

Of interest is that the disease can reactivate even after many years of remission; Figure 4 shows remission durations in patients who subsequently had reactivation of their disease.

Finally, we analyzed remission rates according to the delay in entering our center. Patients who were referred early (< 1 year from disease onset) had a higher remission rate at the last visit than patients referred 1–5 years or > 5 years from disease onset (35.7%, 32.4%, 22.8%, respectively), with a statistically significant linear trend by chi-square test (1 df) (p = 0.0124). This was true also when

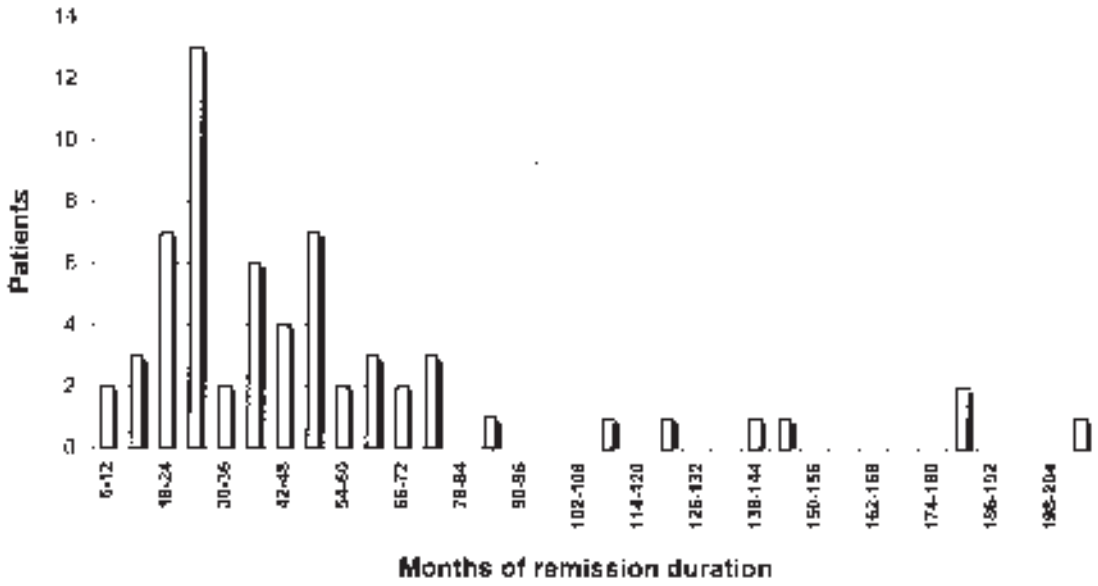

Figure 4. Remission duration in patients whose disease reactivated during the followup.

considering the different disease groups, even if the trend was statistically significant only in the juvenile SpA group (p = 0.009). In particular, if we consider only patients who were referred early to our clinic (< 1 year from disease onset), remission rates were 38.4% (98/255) for oligoarticular JCA, 14.6% (7/48) for polyarticular JCA, 30.5% (11/36) for systemic JCA, and 51.5% (17/33) for SpA. To further investigate the influence on remission rate of delay in attending our center, the cohort was split into 4 groups according to the duration of followup: group A from 1 to 5 years (206 patients), group B 5.1 to 10 years (186 patients), group C 10.1 to 15 years (138 patients), and group D > 15 years (153 patients). Remission rates at the last visit were calculated for each group according to delay in coming to our center. There was a significant trend toward higher remission rates in patients with early (< 1 year) referral, even considering duration of followup. The same trend observed for the whole series was also apparent in the 4 groups of patients, even if the results were statistically less significant, probably due to the small size of the samples.

Of the total group of 683 patients, 529 are still attending the clinic, while 153 (22.4%) have been lost to followup, since they have not been seen for at least 2 years (one girl with systemic onset JCA died at age 17, after 10 years of persistently active disease, with sepsis and renal failure). Comparing these 2 groups (Table 2), we observed no difference in clinical diagnoses. Mean disease duration was significantly shorter in patients lost to followup. Remission rate in patients lost to followup was higher than in patients still attending the clinic (43.1% vs 29.9%; p = 0.002). Considering the different clinical forms, the percentage remission rates were higher in patients lost to followup for all groups. The differences were marked and statistically significant for the oligoarticular group (+14.3%), with a borderline significance for juvenile SpA (+23.4%), while they were minor and not statistically significant for the systemic onset JCA (+11.7%) and polyarticular onset JCA (+4.1%) groups. Of 153 patients lost to followup, the majority (n = 126) had been seen within the first 5 years of disease. Remission rate at the last visit was 46.8% in this group, compared to 26.3% in the 19 patients who had been seen 5–10 years from disease onset and 25% in the 8 patients who had been seen > 10 years after disease onset.

DISCUSSION

Outcome assessment in childhood arthritis has been the focus of studies since the late 1970s[4,5], and has drawn considerable attention up to the present[6-13]. In this regard, remission rates in childhood arthritis are not exactly known. The definition of remission varies between different studies, arthritis classification is a work in progress, and performing longterm studies is hampered because patients can be lost at followup. It has been said that JCA has in general a favorable prognosis, and one paradigm was that 80% of children with JCA would be expected to be rid of inflammation when reaching adulthood[14]. Indeed, the published studies are very heterogeneous in nature. Difficulties in interpreting outcome studies are represented by heterogeneity in patient selection, disease classification, criteria for remission assessment and definition, and type of facility (primary, secondary, or tertiary care center). Population based studies certainly have less selection bias than hospital based studies, which might include the most severe cases[15]. The Italian health system is public and free for all citizens, and primary pediatricians perform mostly primary care, so that it is unlikely that less severe forms of arthritis are not referred to a hospital, unlike other countries. The Gaetano Pini Institute is a tertiary care center that has the advantage of following both adults and children, so that continuity of care allows proper followup and longterm study designs.

The results of this study are in agreement with a recent report[1] in which, after a mean followup of 7 years, the majority of JCA/juvenile SpA patients still had active disease. Also, the percentages of active arthritis in the 3 disease onset types of JCA were similar at followup in the 2 studies. A study from Norway[16] reported more favorable results, with an overall remission rate of 60% after a similar followup period. Less selection in favor of more severe cases was suggested by the authors to explain the better outcome in their series, which consisted of all new cases admitted to hospital over a period of one year. In our study, it is possible that a selection bias in favor of more severe cases was present, since about half the patients were referred

Table 2. Composition and percentage remission rates of patients according to their attendance at our center.

Onset	Patients Still Attending			Patients Lost to Followup			Difference p
	No. Patients	No. Remission	% Remission	No. Patients	No. Remission	% Remission	
Oligoarticular	336	112	33.3	84	40	47.6	0.0292
Polyarticular	84	14	16.7	24	5	20.8	NS
Systemic	62	19	30.6	26	11	42.3	NS
Juvenile SpA	48	14	29.2	19	10	52.6	0.0928
Total	530	158	29.9	153	66	43.1	0.0027
Mean Disease Duration (followup) yrs	10.5 ± 7.2			8.4 ± 6.7			0.0013

not at or for diagnosis, but already during the disease course. Indeed, in our study a delay in attending the tertiary care center seemed to worsen the outcome, since remission was lower in patients referred after a longer time. This is presumably due to selection of cases with refractory disease, but possibly also to a better response to proper early treatment. Similarly to our experience, Zak, *et al*[17] recently reported that longterm outcome of JCA is associated with active disease persisting into adulthood in more than one-third of cases; however, a selection bias toward more severe cases was also present in this study.

We had a relatively low rate of patients lost to followup (22.4%), i.e., they did not come to followup for at least 2 years. We observed a higher remission rate in patients lost to followup: this can reflect a different disease duration in the 2 groups, and/or the fact that patients with milder disease are less likely to seek medical care and keep followup appointments.

Overall, we observed that the remission rate increases with followup time up to 5 years from disease onset, after which it reaches its peak (5–10 years from disease onset), and then slowly declines. This is probably because patients with active disease tend to seek medical advice more frequently, and therefore would stay in the followed group for a longer period. Moreover, we observed that in some patients the disease can reactivate even after a long period (> 15 years in a few cases) of remission.

Classification of childhood arthritis is a work in progress, and new criteria for classification of the so-called juvenile idiopathic arthritides have been proposed by ILAR[18]. For the purpose of this study, we decided to categorize our patients according to the EULAR and ESSG classification, although we acknowledge the importance of the new classification system[19]. This is mainly because roughly 23% of our patients would fall into the nonspecific ILAR category of "other arthritis" and therefore we would have lost a large part of our data.

Our study has shown that remission depends mostly upon clinical diagnosis, and is scarcely influenced by age at disease onset. As expected, RF positive polyarticular disease had the worst prognosis. In the juvenile SpA group, the group less frequently studied, juvenile ankylosing spondylitis had a worse prognosis than psoriatic arthritis and undifferentiated spondyloarthropathy.

Our hospital based study suggests that childhood arthritis goes into remission in about a third of cases. In our series, 58.3% of patients never achieved remission during the disease course. Patients who were referred and treated before one year of disease had a better prognosis concerning remission at last visit. These findings need to be confirmed in other series and with prospective population based studies. These findings could also be important from a therapeutic point of view, as more aggressive treatment can be warranted in selected cases.

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