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Remission status follow-up in children with juvenile idiopathic arthritis

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Abstract

Objective: To characterize articular and systemic inflammatory activity in juvenile idiopathic arthritis (JIA), identifying remission status with and without medication.

Methods: A total of 165 JIA cases, followed for a mean period of 3.6 years, were reviewed in order to characterize episodes of inactivity and clinical remission on and off medication. The resulting data were analyzed by means of descriptive statistics, survival analysis, by comparison of Kaplan-Meier curves, log rank testing and binary logistic regression analysis in order to identify predictive factors for remission or persistent activity.

Results: One hundred and eight of the cases reviewed fulfilled the inclusion criteria: 57 patients (52.7%) exhibited a total of 71 episodes of inactivity, with a mean of 2.9 years per episode; 36 inactivity episodes (50.7%) resulted in clinical remission off medication, 35% of which were of the persistent oligoarticular subtype. The probability of clinical remission on medication over 2 years was 81, 82, 97 and 83% for cases of persistent oligoarticular, extended oligoarticular, polyarticular and systemic JIA, respectively. The probability of clinical remission off medication 5 years after onset of remission was 40 and 67% for patients with persistent oligoarticular and systemic JIA, respectively. Persistent disease activity was significantly associated with the use of an anti-rheumatic drug combination. Age at JIA onset was the only factor that predicted clinical remission ($p = 0.002$).

Conclusions: In this cohort, the probability of JIA progressing to clinical remission was greater for the persistent oligoarticular and systemic subtypes, when compared with polyarticular cases.

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic form of arthritis, the causes of which are unknown, that affects one or more joints. Onset is before 16 years and it lasts for more than 6 weeks consecutively with diagnosis made after other specific diseases that also cause arthritis have been ruled out.[1,2] This is both one of the most common rheumatic diseases in pediatrics and also one of the most common chronic diseases of childhood.[3]

Treatment is complex and has undergone major changes during the last ten years,[4-6] although there is still no single ideal scheme for controlling the disease and modifying its progress. Natural disease progression is characterized by periods of activity and periods of quiescence with unpredictable duration. Recently proposed criteria and definitions of the response or absence of response to treatment have been developed, characterizing a major advance that allows for the comparison of alternative and traditional treatments.[7]

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Cohort studies evaluating JIA prognosis indicate that many children suffer disease activity that lasts into adulthood.[8-15] Using the most recent advances in treatment, periods of inactivity have also been observed, which may then progress to remission or relapse.[16] A consensus on the criteria for JIA remission was reached recently,[16-18] defining different criteria from those for adults.[19]

Clinical remission on medication (CRM) was defined as when a patient exhibits 6 months continuous disease inactivity when on medication, and clinical remission off medication (CR) was defined as 12 months of inactivity off medication.

The objectives of this study were to characterize articular and systemic inflammatory activity, to establish the probability of CRM and CR and to identify predictive factors for remission and persistent activity in a cohort of JIA patients.

Methods

Retrospective analysis was performed of 165 JIA cases treated at the Pediatric Rheumatology Clinic, Botucatu Medical School Hospital, Universidade Estadual Paulista, between 1986 and 2005.

All cases that met the International League of Associations for Rheumatology (ILAR),[1] JIA classification criteria were included if their first visit had taken place between 1986 and 2004 and had been followed at least 1 year.

Case-notes review information was obtained using two data collection protocols. The first collated demographic and clinical data to confirm inclusion criteria were met, and the second contained information necessary to define each inactivity episode.

The criteria adopted to define inactivity and clinical remission were those proposed recently by Wallace et al.,[16] which include:

1) no active arthritis in any joint;
2) no fever, typical rheumatoid rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA;
3) no active uveitis as confirmed by an ophthalmological examination;
4) normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) test (if performed, both tests had to be negative);
5) a physician's global assessment on a visual analogue scale ranging from inactive to very severe, rated at the best score possible.[16]

In our study just the first four criteria were employed, excluding the global evaluation by a physician, since this parameter for evaluation of arthritis activity was not routinely used throughout the study period. Furthermore, ESR and CRP tests were generally requested in response to signs of active arthritis, but were not employed systematically to classify activity or inactivity in stable or controlled patients.

Results are presented in the form of descriptive measures, by comparison of subsets that achieved remission with those that did not, classified by sex, age at onset, medication employed and arthritis subtypes, and analyzed using the Mann-Whitney non-parametric test. The probability of CR and CRM was estimated by survival analysis, taking remission as the event of interest and adjusting curves for each arthritis subtype using the Kaplan-Meier method, to a confidence interval of 95% (95%CI). Comparisons between the resultant curves were made by log rank testing.

Logistic regression analysis was used to assess the relationship between the medications employed and the clinical outcome of inactivity or persistent activity. The same type of model was adjusted stepwise, taking CR as a function of age at first visit, treatment and subtype of arthritis. The level of significance was set up at 5% for all tests.

The data collected were organized in Microsoft Excel 2000 spreadsheets, and statistical analysis was performed using SPSS 12.0, S-Plus 6.2 and SAS 8.02.

This project was approved by the Research Ethics Committee at the Botucatu Medical School Hospital.

Results

Retrospective analysis was performed on 165 medical records, 108 of which met the inclusion criteria, with a mean follow-up period of 3.6 years (1 to 19 years), and a median of 4.6 years.

Table 1 contains demographic and clinical characteristics of each of the subtypes studied, broken down by age at first visit, sex, the presence of antinuclear antibodies (ANA), uveitis and activity or inactivity status during the period under analysis. There were no deaths among the cases analyzed.

Regarding the distribution of cases, 33% had the first clinical visit between 1986 and 1996, and 66,7% more recently, between 1997 and 2004.

From the total of 108 patients, 51 (47.2%) had persistent disease activity throughout the follow-up period. These patients were followed-up for a mean period of 3.6 years (1-19 years) with median of 2.2 years. Fifty-seven (52.7%) patients exhibited at least on episode of inactivity, to a total of 71 episodes, with mean duration of 2.9 years (0-15.5 years). Forty-two percent of the patients (n = 46) had just one disease inactivity episode, 8.3% (n = 9) had two episodes, 0.9% (n = 1) three episodes and 0.9% (n = 1) four episodes. Of the total of 71 inactivity episodes, 36 (50.7%) were CR

episodes. These episodes were preceded by CRM or by inactivity without CRM. Eighteen cases of persistent oligoarthritis, nine of systemic arthritis, four of RF- polyarthritis, three of extended oligoarthritis and one with enthesitis-related arthritis achieved CRM. Twenty-two cases of persistent oligoarthritis, seven of systemic arthritis, three of extended oligoarthritis and two cases of RF- polyarthritis achieved CRM. None of the patients with RF+ polyarthritis or with psoriatic arthritis achieved inactivity during the follow-up. No patient with enthesitis-related arthritis achieved CR, although CRM was achieved in these cases.

Mean duration of disease activity preceding inactivity was 1.5 years (0.1-11 years), with a median of 0.69, and mean duration of inactivity was 2.3 years (0-15.5 years), with a median of 2.3 for all inactivity categories. Mean duration of the first episode of activity was 6.4 years (0.4-15 years) and 0.8 years (0.1-3 years) for the second episode. There was a statistically significant difference between activity duration for the two groups ($p < 0.001$). Duration of the first inactivity episode was 1.6 years (0.8-11.7 years), and for the second episode it was 2.2 years (0-5.6 years), with no statistical difference between these inactivity periods (Mann-Whitney test).

Age at onset of arthritis for the 57 cases that achieved inactivation was 6.9 years (0.4-15 years), and 8.4 years for the 51 cases that did not achieve it (1.3-14.4 years), without significant difference (Mann-Whitney test).

Only patients with persistent oligoarticular, extended oligoarticular, RF- polyarticular and systemic JIA achieved CR. Mean duration of disease activity prior to achieving CR, for each of the above subtypes, was 1 (0.2-5.2 years), 6.1 (0.4-11 years), 1.5 (0.8-2 years) and 0.9 (0.1-2.5 years), respectively, while mean duration of CR episodes was 4.7 (0.8-15.5 years), 3.7 (2-6.4 years), 4.8 (2.3-7.2 years) and 6 (1.6-8.6 years), respectively. There was no statistically significant difference between the groups in terms of activity and inactivity duration (Mann-Whitney test).

Treatment for JIA was classified by subtype and number of joints involved, according to the algorithm proposed by Wallace.[6] All patients received nonsteroidal anti-inflammatory drugs (NSAID). Patients were grouped according to the medication or combination of medications given: group A, monotherapy with NSAIDs; group B, in association with oral steroids, with or without topical treatment for uveitis; and group C, in which patients were on a diverse range of drug combinations: methrotrexate, sulfasalazine, hydroxychloroquine, pulsed methylprednisolone, cyclosporine A, leflunomide, abatacept and infliximab, in addition to intra-articular steroid injection.

The proportion of cases in persistent activity or inactivity was analyzed by logistic regression, comparing groups B and C. There was a significant increase in the proportion of inactivity and significant decrease in the proportion of persistent activity in group B, in relation to group C ($p < 0.0001$).

Survival analysis took JIA subtypes and arthritis activity as events of interest for the outcomes CRM and CR, and is presented in the form of Kaplan-Meier curves estimating the probability of sustaining remission. Patients with the persistent oligoarticular subtype achieved the greatest duration in CRM, with 11% of them attaining more than 6 years' remission. The probability of sustaining CRM for 1 year was 90%; for 2 years it was 81%; and at 3 years it was 68% for these 18 cases. For the extended oligoarticular subtype,

Table 1 - Demographic and clinical characteristics of JIA cases

JIA subtype	n (%)	Age at 1st visit (years), mean ± SD	Sex n (%)		ANA n (%)	HLA-B27 n (%)	Uveitis n (%)	Achieved inactivity (n = 57) n (%)	Persistent activity (n = 51) n (%)
			F	M					
Persistent oligoarticular	63 (58.3)	6.6±3.2	29 (46)	34 (54)	7 (11.1)	0	3 (4.8)	35 (55.6)	28 (44.4)
Extended oligoarticular	9 (8.3)	9.6±3.8	4 (44.4)	5 (55.6)	0	0	1 (11.1)	5 (55.6)	4 (44.4)
RF+ polyarticular	2 (1.8)	12±1.6	2 (100)	0	1 (50)	0	0	0	2 (100)
RF- polyarticular	11 (10.2)	9.7±3.6	10 (90.9)	1 (9.1)	2 (18.2)	0	1 (9.1)	5 (45.5)	6 (54.5)
Systemic arthritis	13 (12)	5.1±3.3	6 (46.2)	7(53.8)	1 (7.7)	0	0	11 (84.6)	2 (15.4)
Psoriatic arthritis	1 (0.9)	5.7	1 (100)	0	0	0	0	0	1(100)
ERA	5 (4.6)	9.1±1.5	0	5 (100)	0	5 (100)	2 (40)	1 (20)	4 (80)
Undifferentiated arthritis	4 (3.7)	7.5±6.2	1 (25)	3 (75)	0	0	1 (25)	0	4 (100)

ANA = antinuclear antibodies; ERA = enthesitis-related arthritis; JIA = juvenile idiopathic arthritis; RF = rheumatoid factor; SD = standard deviation.

1-year probability was 100%, and 2-year probability was 82%, estimated from six episodes. For systemic JIA, 1-year probability was 97% and 2-year was 83%, for 13 cases. For extended oligoarticular and RF- polyarticular subtypes, maintenance of CRM beyond 5 years was negligible, while for persistent oligoarticular JIA it was 44%, and for systemic arthritis it was 49%. Survival analysis with CR as the outcome revealed that 33 (91.6%) of the 36 episodes attained CR for 1 year, but that just 19% sustained CR for more than 5 years. After 1 year, the probability of maintaining CR was 97, 100, 100 and 97%, for the subtypes persistent oligoarticular, extended oligoarticular, RF- polyarticular and systemic arthritis, respectively. After 3 years, these probabilities were 83, 92, 92 and 79%, respectively. These subtypes achieved just 22, three, two and nine episodes of CR, respectively. The chances of CR after 5 years' follow-up were 44% for persistent oligoarticular and 67% for systemic arthritis. For cases with polyarthritis and enthesitis-related arthritis, analysis was limited by the small number of cases attaining CR; three and two, respectively. Frequencies of CR are presented in Table 2.

Kaplan-Meier curves for CRM and CR episodes were compared between the subtypes persistent oligoarticular, extended oligoarticular, RF- polyarticular and systemic arthritis using log rank testing, without identifying statistical differences (Figure 1).

Using stepwise adjusted logistic regression analysis, taking CR as outcome and age at first visit, arthritis subtypes and medication categories as variables, it was observed that only age at first visit was a predictive factor for CR ($p = 0.002$); OR = 0.822; 95%CI 0.723-0.933.

Discussion

The clinical course of JIA and its relationship with clinical remission or persistent activity outcome was analyzed in a historic cohort. All JIA subtypes according to the ILAR[1] classification were included, as long as follow-up was sufficiently prolonged to make it possible to evaluate the chance of arthritis inactivity. The prevalence of each of the subtypes was compatible with rates reported by other authors.[8,9,20]

Eight percent of cases had had uveitis previously. Prevalence rates in published data vary from 6.5 to 46.7%.[8,10,21] Uveitis was related to the prevalence of ANA, which, in our study, was 10.2%, well below the 66% reported by Wallace et al.[20] and the 46.1% described by Zak & Pederson,[11] but comparable with results published by Arguedas[22] for Latin American patients. The antigens HLA-B27 were only tested for in the presence of enthesitis.

Overall mean age at first visit for all subtypes was 8.1 years. It should be noted that age at first visit is not the same as age at onset of symptoms or at diagnosis of JIA, since

Table 2 - Duration of episodes of clinical remission off medication in JIA

	Persistent oligoarticular		Extended oligoarticular		RF- polyarticular		Systemic	
Inactivity episodes	37		9		6		18	
CR episodes	22		3		2		9	
Duration of CR (years)	n	%	n	%	n	%	n	%
1	21	95	3	100	2	100	7	77
2	19	86	2	66	1	50	3	33
3	16	72	1	33	0		2	22
4	13	59	1	33	0		1	11
5	7	32	0		0		0	
15	1	4.5	0		0		0	

CR = clinical remission off medication; RF = rheumatoid factor.

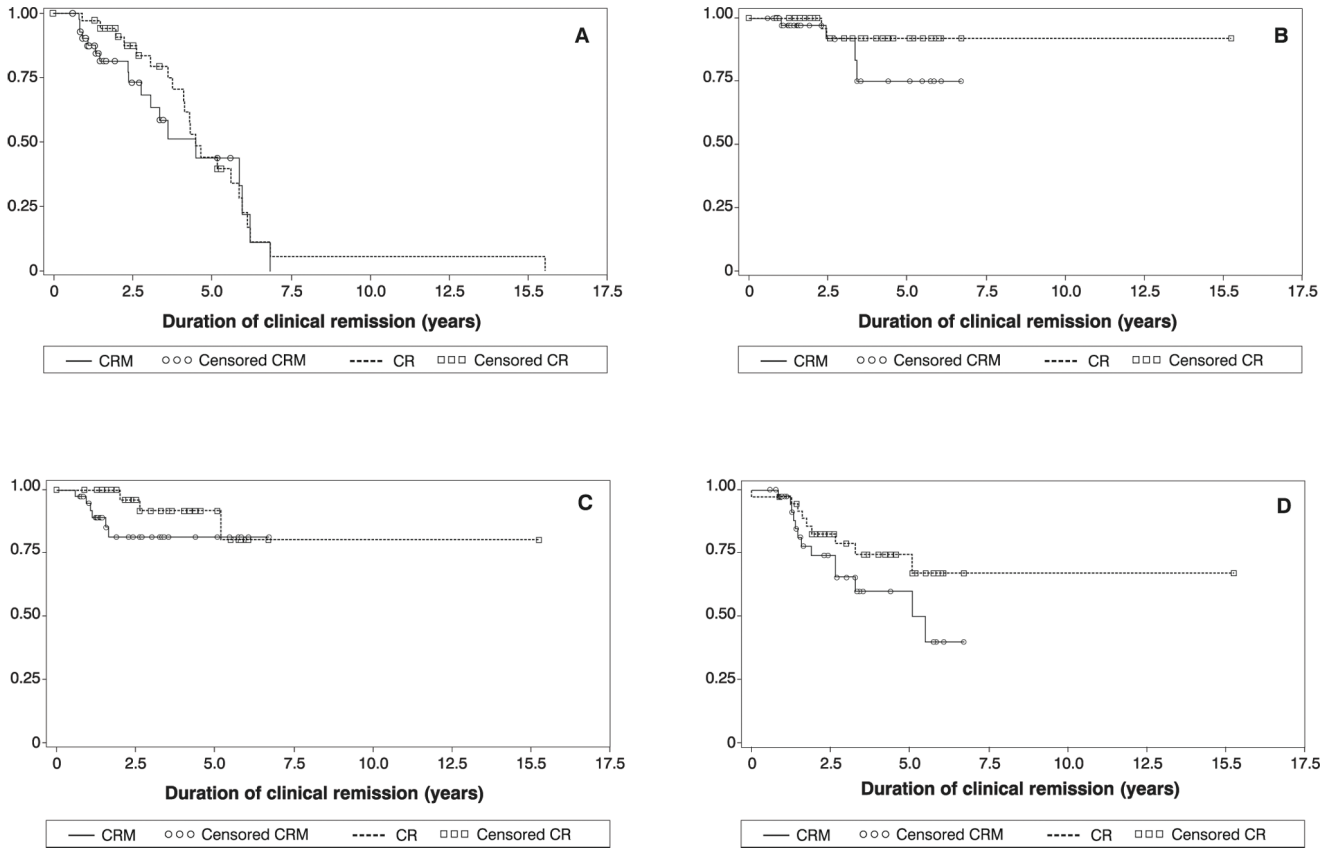

Figure 1 - Comparison between Kaplan-Meier curves for JIA subtypes: A) persistent oligoarticular; B) extended oligoarticular; C) RF- polyarticular; D) systemic
CRM = clinical remission on medication; CR = clinical remission off medication; RF = rheumatoid factor

referral was delayed in many of these cases.[23] Around 1/3 of patients began follow-up between 1986 and 1996, and 2/3 between 1997 and 2004. The distribution of patients by year of disease onset described by Wallace et al.[20] in a 20-year cohort was 18% of cases with follow-up starting during the first decade and 82% in the second decade. In a smaller sample with shorter follow-up duration, we observed a distribution of similar proportions, i.e. a greater number of cases during the second decade. This is probably the result of increased knowledge of JIA, expansion of specialized services and earlier recognition of the signs of arthritis by pediatricians, as stated by Petty,[24] writing on the wide global variation in incidence and prevalence observed by Manners & Bower.[25] In developing countries, pediatric rheumatology is still establishing itself as a referral specialty, and late diagnosis continues to be a problem.[26]

Forty-seven percent of patients maintained persistent activity throughout outpatient follow-up. Patients with persistent activity at 19 years of age were transferred to the adult clinic, and the majority of those who attained remission were followed until they left the pediatric rheumatology clinic.

In 52% of cases at least one period of inactivity was identified during follow-up, totaling 71 episodes, 50.7% of which attained CR, making 33.3% of the total number of cases. In contrast, Wallace et al.[20] describe progression to CR in just 26% of cases, of which patients with persistent oligoarticular JIA sustained inactivity for the longest period. In our study, patients with systemic arthritis maintained inactivity longest.

The natural course of JIA is characterized by periods of activity and quiescence of unpredictable duration. Some cases follow a course of persistent activity or of polycyclic activity, interspersing periods of activity and inactivity, or may be monocyclic, with a single period of activity followed by prolonged or persistent inactivity. Such courses have best been characterized in the systemic form of JIA.[27]

The greater frequency of remission observed for the systemic subtype (52.8%), when compared with other studies using similar definitions of remission (Table 3), may be a result of differences in complexity of the cases. Minden et al.[8] found 47%, while Wallace et al.[20] and Oen et al.[13] found 37%. Singh-Grewal et al.[27] studied a cohort of systemic JIA patients and, employing three different criteria for clinical remission, found that 42.2% of those with monocyclic course, 4.4 to 20% of those with polycyclic course, and 37.8

to 53.4% of the patients with persistent disease course attained inactivity disease on and off medication.

Several investigators have described the remission outcome from JIA in their patient samples.[8,11-14,20,28] Guilhaume et al.[28] studied the oligoarticular form, finding that more than 100 mm in the first hour of ESR, more than one affected joint and upper limb involvement were predictive of a change in course from persistent to extended oligoarticular JIA. Just 23% of their patients attained CR, 50% progressed to the extended oligoarticular form, 35% exhibited articular erosion and 30% exhibited uveitis.

Fantini et al.[12] analyzed a cohort of 683 patients, with a mean follow-up of 10 years. According to the authors, 32.8% of the patients were in remission at their most recent visit. The probability of attaining remission reduced in proportion with the delay in referral to the tertiary service (from 35.7 to 22.8%).

According to Oen et al.,[13] more than 60% of the children with JIA reached adulthood with active arthritis, and 39% achieved CR. Their probability of CR after 10 years was 37, 47, 23 and 6% for the systemic, oligoarticular, RF- and RF+ polyarticular subtypes, respectively. Over 15 years, the probability of relapse was from 30 to 100%. Our data indicate a less promising probability of CR over 5 years, being null for systemic, polyarticular and extended oligoarticular subtypes, and 32% for persistent oligoarticular JIA. Notwithstanding, divergent remission definition was reported.

Minden et al.[8] observed CR in 40% of adults with a diagnosis of JIA, being greater for the oligoarticular subtype (54%), with 73% for the persistent oligoarticular subtype and 12% for extended oligoarticular JIA (Table 3). They concluded that half of their patients exhibited functional and structural repercussions after 15 years of disease activity, but less than 10% progressed to physical disability. The authors used the remission criteria from the American College of Rheumatology (ACR) for rheumatoid arthritis.[19] Table 3 lists frequencies for inactivity and clinical remission by JIA subtype, compared with observed frequencies in recent literature.

There are many studies that demonstrate that patients with JIA reach adulthood with active arthritis, at percentages varying from 20 to 60% of cases, depending on the study realized.[10,11,29] More common among patients with extended oligoarticular or polyarticular forms,[11] many persisted with limitations to their day-to-day activities[15] and exhibited severe functional disability assessed by the Health Assessment Questionnaire (HAQ),[10] varying from 37 to 43%

Table 3 - Frequency of inactivity and clinical remission from JIA, compared with recent literature

	This study	Wallace et al.[20]	Oen et al.[13]	Minden et al.[8]
Mean duration of follow-up	3.6 years	7.7 years*	10 years	16.5 years
Inactivity	52%	89%	56%	47%
Clinical remission	33.3%	26%	39%	40%
Persistent oligoarticular	34.9%	68%	47%†	73%
Extended oligoarticular	33.3%	31%	-	12%
RF+ polyarticular	0	5%	6%	0
RF- polyarticular	18.2%	30%	23%	30%
Systemic arthritis	52.8%	37%	37%	47%
Psoriatic arthritis	0	-	-	33%
Enthesitis-related arthritis	0	-	-	18%

* Patients who attained disease inactivity.
† Persistent oligoarticular and extended oligoarticular included.
RF = rheumatoid factor.

depending on the study. Physical and emotional sequelae are observed among adolescents and adults with persistent disease activity.[29]

We observed that anti-rheumatic drug combination treatment was correlated with persistent activity. There are no controlled pediatric studies of drug combination for arthritis,[5] just open studies with small case series.[30] Severity and extent of arthritis at disease onset, arthritis symmetry, hip and wrist involvement, presence of rheumatoid factor and persistent activity have all been linked with poor JIA prognosis.[31] Our findings regarding anti-rheumatic drug combination hierarchy corroborates these observations.

We conclude that there is a 35% 5-year probability of remission with the persistent oligoarticular subtype, while the remaining forms have a chronic course with relapses. This finding is of importance for planning JIA treatment.

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