

Accuracy of Wallace Criteria for Clinical Remission in Juvenile Idiopathic Arthritis: a Cohort Study of 761 Consecutive Cases

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ABSTRACT. Objective. To evaluate disease course and clinical usefulness in some categories of juvenile idiopathic arthritis (JIA) by applying newly developed Wallace definitions of remission off drugs.

Methods. In a retrospective study, charts of patients with chronic form of primary (idiopathic) arthritis followed from our center since 1970 were reviewed and clinical/laboratory variables were collected for further analysis.

Results. The cohort included 761 eligible patients [516 (67.8%) female, 245 (32.2%) male] with JIA. Mean disease onset age (\pm standard deviation) was 6.25 ± 4.4 years (range 0.5-15.9). Disease mean duration to last visit was 10.02 ± 4.31 years. Followup mean period was 7.6 ± 6.4 years (range 1.5-35 yrs). A total of 247 (32.46%) patients achieved remission according to criteria [persistent oligoarthritis 153 (42.9%); extended oligoarthritis 15 (13.1%); seronegative polyarthritis 21 (22.4%); systemic arthritis 33 (33.7%); enthesitis related arthritis (ERA) plus juvenile psoriatic arthritis (JPsA) 25 (33.4%)]. No patients with seropositive polyarthritis achieved remission status ($p < 0.001$). In remitted patients the mean survival function (\pm standard error of the mean) before relapse calculated by Kaplan-Meier was of 20.9 (± 1.3) months overall: 21.7 (± 0.46) in persistent oligoarthritis, 25.0 (± 6.6) in extended oligoarthritis, 26.7 (± 13.2) in seronegative polyarthritis, and 17.6 (± 2.44) in ERA+JPsA ($p > 0.1$).

Conclusion. In our cohort about one-third of cases obtained a remission episode in 4 decades of observation, with a significant difference between oligoarthritis and other categories ($p < 0.001$) using the Kaplan-Meier method; the remission status duration before a relapse has been about 20 months, without a significant difference between JIA categories. (First Release June 1 2009; J Rheumatol 2009;36:1532-5; doi:10.3899/jrheum.080434)

Key Indexing Terms:
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JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the most prevalent pediatric rheumatic disease among children in North America and elsewhere¹. The term describes a heterogeneous group of childhood diseases that have in common chronic idiopathic inflammation of 1 or more joints. Until recently, complete disease quiescence has been difficult to achieve in most forms of JIA; the majority of children with JIA have continuing or recurrent disease that often extends into adulthood²⁻⁶. Wallace, *et al* recently proposed remission criteria in JIA: patients with JIA may be in 1 of 2 states, active or inactive disease. The criteria for inactive disease include the following: no active arthritis; no fever, no rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation

rate or C-reactive protein level; and a physician's global assessment of disease activity indicating clinical disease quiescence. Inactive disease can be divided further into clinical "remission on medication" (a minimum of 6 continuous mos of inactive disease while receiving medication) and clinical "remission off medication" (12 mos of inactive disease while not receiving any antiarthritis or antiuveitis medication). The finalized criteria for remission off medication ideally should predict that a patient has 20% probability of disease recurrence within the next 5 years⁷. The aim of our study was to attempt to test the accuracy of these criteria, applying them in a large cohort of patients with JIA and focusing attention on duration of the first remission episode off drugs. The end of remission status was defined as the presence of at least 1 active joint for 4 weeks.

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MATERIALS AND METHODS

Patients. All patients diagnosed with a chronic form of primary (idiopathic) arthritis attending our center from 1970 to 2004 were eligible. To be enrolled in the study a minimum followup of 1 year comprehensive of clinical data [age at disease onset, demographic data, family history of psoriasis or autoimmune disease, HLA B27, rheumatoid factor (RF) titers, arthritis distribution, physician assessment, therapeutic variables as disease mod-

ifying antirheumatic drugs dose, and therapy length] was required. Until the year 2000 patients were classified according to the European League Against Rheumatism criteria (juvenile chronic arthritis, JCA)⁸, with the exclusion of patients who satisfied the European Spondyloarthropathy Study Group (ESSG) criteria, who were categorized as having Juvenile spondyloarthropathies (JSPA)⁹. ESSG criteria have been validated also in children by a multicenter European cross-sectional study, to which our group contributed¹⁰. Patients with JCA were categorized in 3 subsets, namely systemic onset JCA, polyarticular onset JCA, and oligoarticular onset JCA. Following the meetings, respectively, in Santiago (Chile) in 1994, Durban (South Africa) in 1997, and Edmonton (Canada), in 2001, a new nomenclature and new classification criteria for juvenile chronic idiopathic arthritides were developed by a Task Force of the International League of Associations for Rheumatology (ILAR). The last revision¹¹ recognizes the following categories under the umbrella of JIA: systemic arthritis; oligoarthritis with 2 subcategories, persistent and extended oligoarthritis; polyarthritis (RF negative); polyarthritis (RF positive); psoriatic arthritis; enthesitis related arthritis; undifferentiated arthritis.

While after the year 2000 the newly enrolled patients were classified according the Santiago-Durban-Edmonton criteria, previously enrolled patients were reclassified according to the new criteria every time this was possible. When difficulty in categorizing a case arose, the hierarchy criterion proposed by us was applied¹². This criterion states that patients with undifferentiated arthritis fulfilling criteria in 2 or more categories are attributed to the category with the highest rank (defined in terms of severity and biological and/or clinical characterization) according to the following sequence: systemic arthritis, seropositive polyarthritis, juvenile spondyloarthritis (including psoriatic arthritis and enthesitis related arthritis), oligoarthritis (persistent or extended), seronegative polyarthritis.

Since the major difficulties in categorizing patients arose for children with psoriatic and/or enthesitis related arthritis, these patients were considered in the same group under the tag of JSPA (ESSG criteria). The actual series encompasses the 683 cases of our previous study on remission¹³. The hierarchy criterion was applied to about 23% of these. Finally, for the purposes of our study the patients were attributed to 6 different categories: systemic arthritis, 98 patients; persistent oligoarthritis, 357 patients; extended oligoarthritis, 111 patients; seronegative polyarthritis, 94 patients; seropositive polyarthritis, 26 patients; JSPA (including psoriatic arthritis and enthesitis related arthritis), 75 patients.

The remission status was defined by an experienced rheumatologist analyzing clinical charts of each patient and applying the Wallace criteria⁷. *Statistical analysis.* Variables were either quantitative or qualitative. Quantitative values were expressed as the mean and standard deviation (SD), and qualitative values as percentages. Comparisons of means and percentages between the different groups were performed with the Student's t-test and the chi-squared test, respectively. Remission rates were calculated by the Kaplan-Meier method and Cox-Snell proportional hazard for the multivariate analysis was calculated. The level of significance was set at $p < 0.05$. All statistics were assessed with SPSS Statistical package for Windows v. 13 (SPSS Inc.).

RESULTS

The cohort included 761 patients (516, 67.8% female; 245, 32.2% male) with JIA (357, 46.9% persistent oligoarthritis; 111, 14.6% extended oligoarthritis; 94, 12.4% seronegative polyarthritis; 26, 3.4% seropositive polyarthritis; 98, 12.9% systemic arthritis; 75, 9.8% JSPA). Mean disease onset age (\pm SD) was 6.25 ± 4.4 years (range 0.5-15.9). Disease mean duration from onset to last visit was 10.02 ± 4.31 years. Followup mean period (starting from first visit to our center) was 7.6 ± 6.4 years (range 1.5-35 yrs). In all populations 263 patients (34.56%) during the study period have been defined

as in remission off medication [persistent oligoarthritis 153, 42.9%; extended oligoarthritis 15, 13.1%; seronegative polyarthritis 21, 22.4%; systemic arthritis 33, 33.7%; enthesitis related arthritis (ERA) plus juvenile psoriatic arthritis (JPsA) 25, 33.4%] (Figure 1). No patients with seropositive polyarthritis achieved remission status. In this subgroup the mean disease onset age (\pm SD) was 5.75 ± 2.4 years (range 1.3-13.2); disease mean duration from onset to last visit was 8.72 ± 2.11 years; followup mean period was 5.2 ± 4.4 years (range 1.5-27 yrs). A significant difference in remission rate was shown between persistent oligoarthritis category and all others also evaluating the variables disease onset age, demographic variables, and disease duration ($p < 0.001$). Persistent oligoarthritis was associated with a Cox hazard ratio of remission of 2.1 ± 1.3 in regard to extended oligoarthritis, 3.7 ± 0.8 in regard to seronegative polyarthritis, 1.2 ± 0.8 in regard to systemic arthritis, and 2.1 ± 0.3 in regard to ERA+JPsA. By Kaplan-Meier survival analysis focused on patients in a remission off drugs status, the mean (\pm standard error of the mean) duration before a disease relapse was 20.9 ± 1.3 months: more precisely, 75% of our patients were in sustained remission after 12.7 ± 0.99 months and 25% after 24.7 ± 2.38 months. Finally, our model estimated $78 \pm 2.7\%$ of patients in remission at 12 months. No significant difference was present in remission length between each category by a log rank test ($p > 0.1$) (Figure 2). Data about seropositive polyarthritis are not shown because in our population no one fulfilled remission criteria during the entire study period. Data about systemic arthritis are not shown because of all patients who fulfilled remission criteria, no one relapsed for the entire observation period (Table 1). These 2 JIA categories were thus excluded from survival analysis.

DISCUSSION

The term *remission* is used extensively in publications of JIA therapy and outcome.

In the literature, patients followed for a mean of at least 10 years have documented varying frequencies of remission, from 29% to 78% for patients with oligoarthritis, 36% to 75% for patients with systemic onset, and 53% to 65% for those with polyarthritis. One recent comparable study using Kaplan-Meier survival curves estimated 10 year remission rates of 38% and 54% for systemic and oligoarthritis JIA (excluding patients with JSPA). An extended polyarticular disease course in patients with pauciarticular JRA has been correlated with a worse prognosis in previous studies. A recent publication estimates the risk of extension at 30% within the first 2 years of disease¹⁴⁻²².

Fantini, *et al*¹³ reported retrospective data for 683 patients with JCA, with a median followup of 8.8 years (range 0.6-36.6 yrs). The population analyzed in our study also includes these patients. The definition of remission used by these investigators required only that a patient was

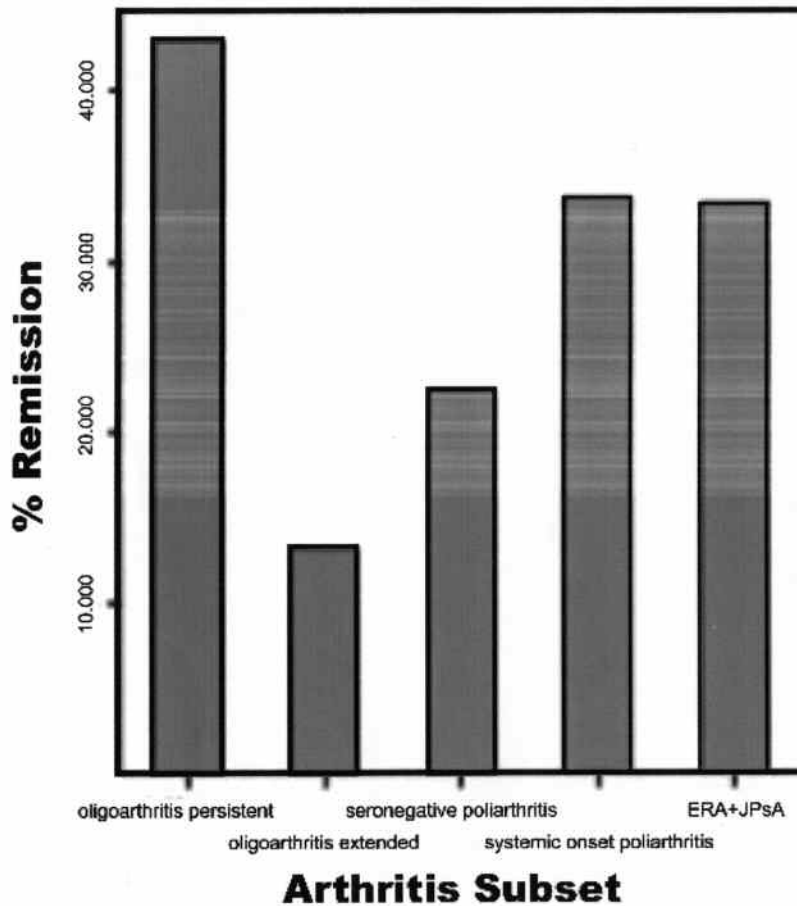


Figure 1. Percentage of patients in each arthritis subset that achieved a remission status.

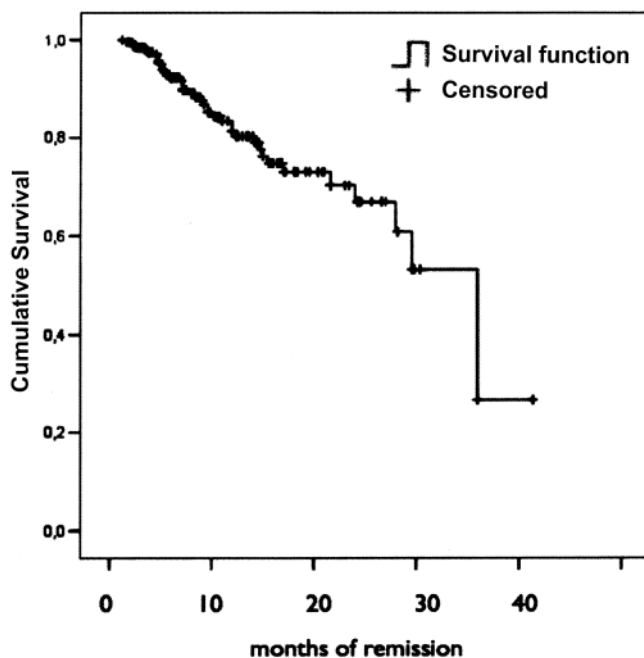


Figure 2. Survival charts by Kaplan-Meier in the whole population. Time periods have at least 25 patients at risk.

off medication for 6 months and did not mention uveitis. Thirty-six percent of patients with pauciarticular arthritis, 17.6% of those with polyarticular arthritis, 32.9% of those with systemic arthritis, and 35.8% of those with JSPA achieved disease remission. In our study we used the criteria proposed by Wallace, *et al*⁷ to determine the prognosis of JIA in each category. These criteria were not originally developed for ERA and PsA, but we maintained these categories for a more complete description of the population. A recent study by Wallace, *et al* using the same remission criteria shows analogous results, reporting that only 36% of remission episodes were sustained for 2 years and only 6% for 5 years²². Participants in the consensus conference had hoped that the criteria for complete remission would identify those patients who had an 80% chance of remaining in complete remission for 5 years⁷. Data presented here and in the literature suggest that this was far too optimistic.

Our approach clearly has some bias: it includes patients with more recent disease onset who would have been treated more aggressively, as well as patients with disease onset in earlier decades whose initial treatment reflected standards of that time and in whom more recent treatment may have included newer therapies. As with all retrospective followup studies, there is the potential for bias toward patients with

Table 1. Observed length of sustained remission in months (\pm standard error, SE) for 25%, 50%, and 75% of patients in each category (log-rank test $p > 0.1$).

Edmonton Categories	25.0% of Patients		50.0% of Patients		75.0% of Patients	
	Estimate	SE	Estimate	SE	Estimate	SE
Persistent oligoarthritis	19.9	0.144	18.7	0.459	10.9	1.254
Extended oligoarthritis	27.5	5.4	25.0	6.628	15.0	4.654
Polyarthritis	35.0	11.7	26.7	13.289	8.3	4.743
Seronegative SpA	19.3	3.256	17.6	2.448	13.4	0.669
Overall	24.7	2.383	18.7	0.569	12.7	0.999

SpA: spondyloarthropathies.

more severe disease involvement being followed up more closely and thus, more likely to be included in longterm followup studies. Further, the Gaetano Pini Institute is a tertiary center for rheumatic pediatric diseases. Finally, our investigation assessed only clinical remission and was not able to utilize imaging techniques to ensure full biologic quiescence of disease. In our cohort only one-third of the patients have been defined as in remission off medications, with a significant difference between the remission rate of persistent oligoarthritis compared to all other categories ($p < 0.001$), also after correction for confounding variables. This finding confirms the literature review. Patients with seropositive polyarthritis did not achieve remission off drugs during the entire observation period. On the other hand, patients with systemic arthritis who reached a remission status did not relapse during the entire observation period, and so we were unable to utilize data from these categories for a survival analysis. Surprisingly, in patients who fulfilled the remission off drugs criterion, the Kaplan-Meier survival curve analysis showed a mean remission period of almost 20 consecutive months before relapse, without significant differences between JIA categories. The small percentage of patients in clinical remission off medications was disappointing, as was the lack of durability of this state.

Our study highlights the urgent need for improved treatments of JIA as well as for longterm prospective studies.

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