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 (± 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 (± 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)

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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)\(^9\), 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 contributed\(^10\). 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 idio-
pathic arthritides were developed by a Task Force of the International
League of Associations for Rheumatology (ILAR). The last revision\(^11\) rec-
ognizes the following categories under the umbrella of JIA: systemic arthri-
tis; oligoarthritis with 2 subcategories, persistent and extended oligoarthri-
tis; polyarthritis (RF negative); polyarthritis (RF positive); psoriatic arthri-
tis; 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 crite-
rian proposed by us was applied\(^12\). This criterion states that patients with
undiifferentiated arthritis fulfilling criteria in 2 or more categories are attrib-
uted 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 polyarthritides, juvenile spondy-
lotharthritis (including psoriatic arthritis and enthesitis related arthritis),
oligoarthritides (persistent or extended), seronegative polyarthritides.

Since the major difficulties in categorizing patients arose for children
with psoriatic and/or enthesitis related arthritis, these patients were consid-
ered in the same group under the tag of JSPA (ESSG criteria). The actual
series encompasses the 683 cases of our previous study on remission\(^13\). The
hierarchy criterion was applied to about 23% of these. Finally, for the pur-
oposes of our study the patients were attributed to 6 different categories: sys-
temic arthritis, 98 patients; persistent oligoarthritides, 357 patients; extended
oligoarthritides, 111 patients; seronegative polyarthritides, 94 patients; seropos-
itive polyarthritides, 26 patients; JSPA (including psoriatic arthritis and enthe-
sitis related arthritis), 75 patients.

The remission status was defined by an experienced rheumatologist
analyzing clinical charts of each patient and applying the Wallace criteria\(^7\).

The cohort included 761 patients (516, 67.8% female; 245, 32.2% male) with JIA (357, 46.9% persistent oligoarthritides; 111, 14.6% extended oligoarthritides; 94, 12.4% seronegative polyarthritides; 26, 3.4% seropositive polyarthritides; 98, 12.9% systemic arthritis; 75, 9.8% JSPA). Mean disease onset age (± 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 oligoarthritides 153, 42.9%; extended oligoarthritides 15, 13.1%; seronegative polyarthritides 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 polyarthritides achieved remission status. In this subgroup the mean disease onset age (± 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 oligoarthritides category and all others also evaluating the variables disease onset age, demographic variables, and disease duration (p < 0.001). Persistent oligoarthritides was associated with a Cox hazard ratio of remission of 2.1 ± 1.3 in regard to extended oligoarthritides, 3.7 ± 0.8 in regard to seronegative polyarthritides, 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 (± 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 ± 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 polyarthritides 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.

**RESULTS**

The remission status was defined by an experienced rheumatologist
analyzing clinical charts of each patient and applying the Wallace criteria\(^7\).

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.).

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**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 remis-
sion, from 29% to 78% for patients with oligoarthritis, 36% to 75% for patients with systemic onset, and 53% to 65% for those with polyarthritides. One recent comparable study using Kaplan-Meier survival curves estimated 10 year remission rates of 38% and 54% for systemic and oligoarthritides 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 disease\(^14-22\).

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
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 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 years. 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 years. 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...
more severe disease involvement being followed up more closely and thus, more likely to be included in long-term follow-up 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 long-term prospective studies.

REFERENCES