Remission in juvenile idiopathic arthritis

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ABSTRACT
Until recently, no uniform and widely accepted criteria for defining remission in juvenile idiopathic arthritis (JIA) were available. In recent years, a set of preliminary criteria for clinical remission in JIA was developed through an international collaborative effort. These criteria enable the classification of patients in the states of inactive disease, clinical remission with medication, and clinical remission without medication. The first phase of the validation process of the criteria, which was accomplished recently, established that they are feasible and have good face, content and construct validity, and strong discriminant properties. A few studies have applied the new remission criteria in series of patients with JIA, with results that concur with those of previous surveys in showing that only a few patients with JIA have a chance of remaining in long-term remission status without medications. These findings highlight the critical need for therapies that have the capacity to induce sustained complete disease control of JIA.

Introduction

In the past, there was a belief that as many as 80% of children with juvenile idiopathic arthritis (JIA) could expect to be free of inflammation when they reached adulthood, which implied that JIA was a benign disease (1). This optimistic view was, however, challenged by the outcome studies published over the years, which showed that the majority of children with JIA had continuing or recurrent disease activity that often extended into adulthood (2, 3). Indeed, although a potential for spontaneous recovery exists in many children with JIA, until recently complete disease quiescence has been difficult to achieve in most forms of JIA, and no medication has been demonstrated to be effective for inducing remission in the majority of patients.

With the shift toward early aggressive interventions and the development of new therapeutic agents and combination treatment strategies, more children with JIA are likely to experience prolonged periods of low levels of disease activity or even complete remission. These advances in therapeutic effectiveness create a need for standardized and widely accepted criteria that describe with sufficient precision the clinical state of disease remission.

Although the matter of complete disease quiescence has been addressed in many studies of JIA therapy and outcome, the term "remission" has been used inconsistently, and for many years there has been a lack of uniform, validated criteria for defining remission. For example, analysis of 24 papers dealing with remission in childhood chronic arthritis published in 2000-2001 revealed that only 3 used the same definition of remission (4). In recent years, this gap was filled through an international collaborative effort that resulted in preliminary criteria for clinical remission in JIA (4).

The preliminary criteria for clinical remission in JIA

The project that led to development of remission criteria for JIA (4) was begun in 2002 and was conducted using consensus formation methodologies that included the Delphi questionnaire approach and Nominal Group Technique. In the first phase, two sequential questionnaires were sent to a large number of senior, clinically active, pediatric rheumatologists. The first questionnaire asked for signs and symptoms that should be considered when determining whether a patient with JIA had achieved clinical remission. Furthermore, it asked how long a patient had to have discontinued all antiarthritis medications in order to be considered in clinical remission without medication. Items listed by more than 80% of respondents were considered to have

reached consensus for inclusion in a definition of clinical remission for JIA. Items mentioned by more than 10%, but fewer than 80%, of respondents were included in a second questionnaire, which was directed to clarifying responses on the initial questionnaire. Overall response rate to the first questionnaire was 130/246 (53%), with respondents representing 34 countries. After completion of the surveys, a 2-day consensus conference was held in May 2003, which was attended by 20 senior pediatric rheumatologists from 9 countries. The goal of the meeting was to reach consensus, through the use of the Nominal Group Technique, on preliminary criteria for inactive disease, clinical remission with medications, and clinical remission without medications.

The conference participants felt that a patient should exhibit a minimum duration of an inactive disease state prior to declaring either form of clinical remission achieved. It was established that inactive disease with medication should persist for at least 6 months before clinical remission while taking medication could be achieved. Similarly, classification of a patient in a state of clinical remission without medication was felt to require persistence of inactive disease for a minimum of 12 months after discontinuation of all anti-inflammatory, antirheumatic, and anti-uveitis medications. Preliminary criteria for inactive disease and clinical remission of JIA, which were agreed upon in the consensus conference, are presented in Table I.

The consensus conference left some unresolved issues. Although all attendees indicated the presence or absence of uveitis as an important item to be included in the criteria, it was decided that pediatric rheumatologists are not the appropriate specialists to determine criteria for inactive uveitis. It was recommended that until a proper definition is available, pediatric rheumatologists should rely upon the judgment of the ophthalmologist who cares for their patients. Additional items that were believed to be potentially important for inclusion in a definition of inactive disease but for which consensus was not

Table I. Preliminary criteria for inactive disease and clinical remission of JIA.

Inactive disease

1. No joints with active arthritis[a,b]

2. No fever, rash, serositis, splenomegaly, or generalized lymphoadenopathy attributable to JIA

3. No active uveitis (to be defined)

4. Normal ESR or CRP (if both are tested, both must be normal)

5. Physician's global assessment of disease activity indicates no disease activity (i.e., best score attainable on the scale used)

Clinical remission

Two types of clinical remission are proposed:

1. Clinical remission with medication. The criteria for inactive disease must be met for a minimum of 6 consecutive months while the patient is taking medication.

2. Clinical remission without medication. The criteria for inactive disease must be met for a minimum of 12 consecutive months while the patient is off all anti-arthritis and anti-uveitis medication.

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; JIA: juvenile idiopathic arthritis.
[a]As defined by the American College of Rheumatology: A joint with swelling not due to bony enlargement or, if no swelling is present, limitation of motion accompanied either by pain on motion and/or tenderness. [b]Isolated finding of pain on motion, tenderness, or limitation of motion on joint examination may be present only if explained by either prior damage attributable to arthritis that is now considered inactive, or nonrheumatologic reasons such as trauma.
(Adapted from: Wallace *et al*. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004; 31: 2290-4).

achieved are the presence of rheumatoid nodules, hepatomegaly, and morning stiffness. It was agreed that a decision about inclusion or exclusion of these criteria should be made after analysis of their statistical performances in the validation phase of the study. The first phase of the validation process of remission criteria recently has been accomplished (5). Using the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter (6, 7), three components (truth, discrimination, and feasibility) were examined in five categories of JIA: systemic arthritis, persistent and extended oligoarthritis, and rheumatoid factor (RF)-positive and -negative polyarthritis. The validation analysis was based on data obtained from the Delphi questionnaire survey, the results of the consensus conference, a retrospective review of 437 patients with JIA who had been followed in 3 tertiary care centers, and the literature. Truth components of face and content validity were ensured by Delphi questionnaire surveys and consensus conference, whose participants reached a consensus level of 80% concerning the variables included in the remission criteria.

In the absence of a "gold standard" for inactive disease in JIA, criterion validity was established by estimating con-

current and construct validity as surrogates. Overall construct validity was determined by demonstrating, through correlation analyses, that the criteria converged to a large extent with other previously published criteria designed to define remission in JIA. Using data from the chart review, the criteria were found to have good discriminating properties, as shown by high levels of classification, prognosis, and responsiveness to clinically relevant change. Remission criteria were found to be feasible because they can be easily, quickly, and inexpensively assessed in the clinic, and present minimal risk to the patient.

Studies of remission in JIA

Remission is a fundamental aspect of long-term outcome studies, as active disease persisting into adulthood is one of the greatest problems JIA patients may face. Furthermore, it is well known that the more persistent the synovitis, the greater the risk of joint destruction, particularly as the skeletal system becomes mature (1). As noted above, until recently standardized and validated remission criteria for JIA did not exist, and consequently, the term was used inconsistently in clinical studies, making comparisons of remission rates difficult. Nevertheless, outcome studies

published after the 1960s have been quite concordant in revealing lower than expected probabilities of long-term disease remission among patients with JIA, with most patients having persistently active disease at last follow-up visit or when reaching the adult age (2, 3). Even limiting the analysis to the studies published over the past 10 years, which are likely to reflect the positive impact of the recent therapeutic advances, the percentage of patients with clinical remission or inactive disease at follow-up ranges from 40% to 60% (3), much lower than the 80% claimed in the past (see above) (Table II). These figures indicate that many JIA patients still enter adulthood with persistently active disease.

JIA is a heterogeneous disease entity that includes conditions that are clinically distinct and have different natural histories (8, 9). Therefore, it is likely that the prognosis of the diverse subtypes is not uniform. Unfortunately, most of the previous studies have not separated the disease subsets. Those investigators who have stratified patients by onset category, however, have found that the outcome differs between the categories. In studies published in the past 10 years (3), the percentage of patients in clinical remission at last follow-up ranges from 33% to 80% for systemic arthritis; 0% to 15% for RF-positive polyarthritis; 23% to 46% for RF-negative polyarthritis; 12% to 35% for extended oligoarthritis; and 43% to 73% for persistent oligoarthritis. These findings indicate that the long-term outcome is best in persistent oligoarthritis and worst in RF-positive polyarthritis. Furthermore, the outcome of systemic arthritis is widely variable, perhaps reflecting the considerable heterogeneity of this JIA subtype.

A number of studies have attempted to identify early predictors of clinical remission in JIA (10). Minden *et al.* (11) found that age at onset and laboratory indicators of inflammation at onset had no association with the probability of remission, while HLA-B27-positive patients with oligoarthritis and late onset (age > 6 years) of disease had a statistically significantly lower likelihood of remission. They suggested that these

Table II. Percentage of JIA patients with clinical remission/inactive disease at follow-up in the outcome studies published after 1994.

Citation	No. of patients	Mean/median disease duration (years)	% of patients with remission/inactive disease
Andersson-Gare, 1995	124	7.1	60
Koivuniemi, 1999	30	7.8	60
Zak, 2000	65	26.4	63
Minden, 2002	215	16.5	45
Oen, 2002	392	10.5	56
Packham, 2002	246	28.3	57
Fantini, 2003	683	8.8	58
Flato, 2003	268	14.9	50
Foster, 2003	82	21	61

JIA: juvenile idiopathic arthritis
Adapted from Ravelli A. Toward an understanding of the long-term outcome of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2004; 22: 271-5.

patients may have juvenile spondyloarthropathy, despite not fulfilling criteria for spondyloarthropathy. Fantini *et al.* (12) found no differences in the rate of remission by sex or age at onset, while patients who were referred early (< 1 year from disease onset) had a significantly higher remission rate at the last visit. Flato *et al.* (13) reported that young age at onset, DRB1*08, positive IgM RF, persistently elevated erythrocyte sedimentation rate (ESR), and large number of affected joints within the first 6 months were risk factors for the absence of remission at follow-up. Among patients with systemic disease, the frequency of remission was found to be 100% (by definition) in those with a monocyclic course, 37% in those with intermittent course, and 23% in those with persistently active course (14). Joint symmetry and ESR ≥ 20/hour in the first 6 months were significantly associated with lesser likelihood of developing clinical remission in patients with oligoarticular-onset JIA (15). However, although considerable information has been accumulated on prognostic factors in JIA, prediction of disease remission remains quite imperfect.

Studies that used newly developed remission criteria

The study by Wallace *et al.* (16) was the first to apply the newly defined criteria for clinical remission in JIA (4). The aim of this investigation was to characterize patterns of disease activity during a prolonged follow-up period in

a large cohort of children with JIA followed in 3 tertiary care pediatric rheumatology centers in the United States and Italy. The design of this study, which focused on sequential time periods of active and inactive disease during the follow-up period, differed from that of previous analyses, which investigated the rate of remission at a single point in time, such as the last follow-up visit or reaching an adult age. Each patient disease course was described in terms of percent time spent in states of active disease, inactive disease, clinical remission with medication, and clinical remission without medications.

A total of 437 patients, in the categories of persistent and extended oligoarthritis, RF-positive and -negative polyarthritis, and systemic arthritis, were included in the study. Patients treated with intra-articular injections alone were excluded. As many as 391 patients (89%) experienced a total of 878 episodes of inactive disease, with a median episode length of 12.7 months (interquartile range [IQR] 4.7-28.3 months). Of the 878 episodes of inactive disease, 228 (26%) resulted in clinical remission without medication. The overall median duration of active disease preceding inactive disease was 20 months (IQR 12-39 months) for the first episode, but decreased to 10 months (IQR 5-19 months) for subsequent episodes. Patients with persistent oligoarthritis had a significantly shorter duration of active disease before the first episode of inactive disease than did

patients with other disease subtypes. Overall, 194 patients (44%) achieved clinical remission while taking no medication at least once during follow-up. Patients with RF-positive polyarthritis were the least likely to achieve clinical remission without medications (5%), whereas 68% of patients with persistent oligoarthritis attained this state. A calculation of the cumulative percent time during follow-up spent in each disease state indicated that, among all patients, the median time spent in a state of inactive disease was 40% (IQR 16%-64%). The median percent time spent in a state of clinical remission while taking medication and with no medication was 4% (IQR 0%-15%) and 0% (IQR 0%-16%), respectively. For both parameters, figures were best for patients with persistent oligoarthritis.

To address the question of what achievement of clinical remission without medication means in terms of prognosis, the authors investigated the likelihood of remaining in clinical remission without medication for 12-month periods using life-table estimates. The results showed that once clinical remission without medication was attained (228 episodes), it lasted an additional year in 77% of episodes for patients with systemic arthritis, 67% of episodes for patients with persistent oligoarthritis and RF-negative polyarthritis, 57% of episodes for patients with persistent oligoarthritis, and no episodes for patients with RF-positive polyarthritis. In the entire patient cohort, only 6% of episodes of clinical remission without medication lasted 5 years or longer. Importantly, patients who were able to attain clinical remission without medication remained disease-free for substantially longer periods than did those who attained only inactive disease or clinical remission while taking medication. Therefore, the remission categories that follow the occurrence of inactive disease may have some prognostic value.

In summary, this study found that among 434 patients with JIA, only one fourth of 878 episodes of inactive disease resulted in clinical remission without medication during follow-up of at least 4 years. In keeping with the results of previous studies, children with persistent oligoarthritis spent relatively more time in a state of inactive disease, whereas those with RF-positive polyarthritis spent the least amount of time in a favorable status. Of paramount importance was the finding that clinical remission without medication was not sustained over more than 1 year, with only 58% sustained over 1 year and a small proportion (6%) sustained over 5 years. This observation confirms that only a few patients with JIA have a chance of remaining in long-term remission and highlights the critical need for therapies that may have the capacity to induce sustained, complete control of this disease.

Recently, Lurati *et al*. (17) applied the newly developed remission criteria in 761 JIA patients followed since 1970 in their unit. Duration of sustained remission after the first episode of inactive disease and accuracy of criteria in predicting long-term outcome were evaluated through review of patient clinical charts. A total of 263 (34.6%) patients achieved clinical remission without medication, including 62.7% in persistent oligoarthritis, 7.6% in extended oligoarthritis, 9.2% in RF-negative polyarthritis, 20.4% in systemic arthritis, 44.8% in enthesitis-related arthritis and psoriatic arthritis combined, and 0% in RF-positive polyarthritis. The mean survival time before relapse, calculated by life-table analysis, was 20.9 months in the entire patient cohort, 18.7 months in persistent oligoarthritis, 25.0 months in extended oligoarthritis, 26.7 months in RF-negative polyarthritis, and 17.6 months in ERA and psoriatic arthritis combined. This study confirmed that the current outcome of JIA is not satisfactory, with only one third of cases being found to have achieved the remission status free of medications over 4 decades of observation. Similarly to the above study, the mean duration of sustained remission after the first episode of active disease was about 20 months.

Singh-Grewal *et al*. (18) investigated whether the disease course in systemic JIA can be described as monophasic, polycyclic, or persistent using three different sets of remission criteria, two of which (clinical remission with and without medication) were derived (with exclusion of the physician global assessment) from the preliminary definition of clinical remission. The third definition was based on authors' experience and required inactive disease to be present for a minimum of 3 months without medication to establish remission. The authors also aimed to identify early predictors of disease course and time to remission.

The majority of the 45 patients were found to have persistent (51.1%) or monophasic (42.2%) course, with only a very small proportion (6.7%) having polycyclic disease. Fever and arthritis at 3 months and an elevated ESR and corticosteroid use at 6 months were predictive of a non-monophasic course. Absence of active arthritis, a normal ESR, and no requirement of corticosteroid therapy at 3 and 6 months were predictors of an earlier time to remission. The definition of remission without medication for 3 months was almost equally sensitive and specific as the correspondent definition requiring a longer time duration (12 months). Therefore, the authors speculated that the former definition, which has the advantage of being applicable much earlier in the disease course, may be more suitable to define the disease courses in JIA.

Future directions
The availability of internationally agreed upon and validated criteria for clinical remission in JIA represents a major advance that provides pediatric rheumatologists with a common vocabulary to describe the same clinical condition. An important merit of this definition is that it recognizes that establishment of remission over time, particularly after discontinuation of antirheumatic medications, is more meaningful than remission at just one time point. The application of the new criteria in future clinical trials will help evaluate in a standardized way whether and to what extent new medications and new therapeutic approaches have the potential for inducing extended periods of disease quiescence, and will enable comparison of results across tri-

als. Furthermore, the new definition offers an easy to use and powerful instrument for assessing accurately the clinical state of patients in daily practice, and in the context of studies of pharmacogenetics, pharmacogenomics, long-term outcome, or disease pathogenesis. As recommended by the investigators who led the development process, the preliminary criteria represent a first step of a work in progress, and several issues must be addressed before they gain widespread use (4). The criteria were designed to cover only select categories of JIA, which include oligoarthritis, polyarthritis, and systemic arthritis. Future studies should investigate the applicability of criteria to the categories of enthesitis-related arthritis, psoriatic arthritis, and other arthritis in order to develop a more comprehensive definition of clinical remission that encompasses all forms of JIA. Furthermore, it is unclear whether patients with persistent oligoarticular disease who are treated with only intra-articular steroids deserve a distinct set of criteria.

Surveys that examined the new criteria are retrospective and are, thus, subject to a significant risk of missing and erroneous data; furthermore, since they are hospital-based there is the potential bias toward inclusion of patients with more severe disease. Prospective studies with predefined times of follow-up assessments and analysis of population-based cohorts are needed to complete the validation process. This process should also address the issue of whether the time durations arbitrarily selected to define the clinical remission with and without medication (6 and 12 months, respectively) are the most appropriate or whether different time intervals (e.g., 24 months for clinical remission without medication) can be more powerful to predict the patient's chance of remaining in long-term complete remission.

Another potential limitation of the criteria is that they assess only "clinical" remission and do not request use of imaging techniques (19) to ensure that remission translates into lesser joint damage. Reports in adult rheumatoid arthritis have shown that radiologic progression can occur among patients

classified as in remission by the American College of Rheumatology (ACR) preliminary criteria (20). Additional investigation will determine whether clinical remission without medication, as defined in the criteria, corresponds to inactive disease as documented by imaging studies. Physical function is another important consequence of JIA activity that is ignored in the criteria. Because improvement of functional ability is one of the ultimate goals of treatment (21) and is of foremost importance to the patients and their parents, the relationship between achievement and durability of remission and prevention of irreversible functional impairment needs to be documented in future studies. As suggested for adult rheumatoid arthritis (22), lack of radiographic progression and a normal functional status might deserve consideration, in addition to the absence of signs of inflammatory activity, as potential criteria for defining remission in JIA.

A further criticism that may be raised to the new remission criteria is that they are based only on physician-centered outcomes (23, 24) and a laboratory measure of inflammation, whereas patient self-reported and parent proxyreported measures (23, 25) are neglected. Although it is unclear whether and to what extent physicians and patients/parents agree in defining remission in JIA, a number of studies have shown that they often disagree in assessing different aspects of disease activity, particularly pain (26-28). Reports in adult patients with rheumatoid arthritis have found that pain (29) has the highest positive predictive value for remission and ESR the lowest (30, 31). Analyses of correlation with patient/parent-centered measures, such as overall well-being, pain, and health-related quality of life scales, will add considerably to the overall construct validity of the criteria during prospective validation. These analyses will help verify whether the term "clinical remission" of JIA can have a clearly understood meaning for our patients and their parents.

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