Preliminary Criteria for Clinical Remission for Select Categories of Juvenile Idiopathic Arthritis

CAROL A. WALLACE, NICOLINO RUPERTO, and EDWARD H. GIANNINI for the Childhood Arthritis and Rheumatology Research Alliance (CARRA), The Pediatric Rheumatology International Trials Organization (PRINTO), and The Pediatric Rheumatology Collaborative Study Group (PRCSG)

ABSTRACT. ***Objectives.*** To develop preliminary criteria for inactive disease and clinical remission for select categories of juvenile idiopathic arthritis (JIA), and to decide what such clinical states should predict in terms of probability of disease recurrence.

Methods. A Delphi serial questionnaire consensus-formation approach was used initially to gather criteria in use by pediatric rheumatologists (PR) for defining clinical remission in oligoarticular (persistent and extended), rheumatoid factor (RF) positive and negative polyarticular, and systemic JIA. Results from sequential questionnaires provided an agenda for a nominal group technique (NGT) conference to reach consensus on unresolved questions.

Results. One hundred and thirty PR from 34 countries responded to the questionnaires and 20 PR from 9 countries attended the conference. Draft criteria for inactive disease include the following: no active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal erythrocyte sedimentation rate or C-reactive protein; and a physician's global assessment of disease activity rated at the best score possible for the instrument used. According to consensus vote, 6 continuous months of inactive disease on medication defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis (and anti-uveitis) medications defines clinical remission off medication. The finalized criteria for remission off medication ideally should predict that a patient has ≤ 20% probability of disease recurrence within the next 5 years.

Conclusion. Using consensus formation techniques, we formulated preliminary criteria for inactive disease and clinical remission on and off medication for use in select categories of JIA. Retrospective validation is in progress; prospective validation will follow. Future efforts will include other categories of JIA. (J Rheumatology 2004;31:2290–4)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS REMISSION CRITERIA

Juvenile idiopathic arthritis (JIA) is the most prevalent pediatric rheumatic disease among children in North America and elsewhere[1]. The term describes a heterologous group of childhood diseases that have in common chronic idiopathic inflammation of one or more joints. JIA encompasses several disease categories with diverse signs, symptoms, and genetic complexity. Our work focuses on several categories of JIA including oligoarticular (< 5 joints involved) (persistent and extended), rheumatoid factor (RF) positive and negative polyarticular (≥ 5 joints involved with or without RF), and systemic JIA, characterized by arthritis, fever, and at least one extraarticular manifestation (such as evanescent rash, lymphadenopathy, hepatomegaly, splenomegaly, or serositis).

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 adulthood[2-9]. With the development of new therapeutic agents and combination treatment strategies, more children with arthritis can experience protracted periods of low levels of disease activity and, in a limited number of cases, complete disease quiescence. These advances in therapeutic effectiveness create a need for the development of validated criteria that describe more precisely the clinical state of disease quiescence[10-15]. Such criteria should consist of a comprehensive set of clinical descriptors relevant to JIA. Criteria

From the Children's Hospital and Regional Medical Center, Department of Pediatrics, University of Washington School of Medicine, Seattle, Washington, USA; the Pediatric Rheumatology InterNational Trials Organization, IRCCS G. Gaslini, Pediatria II, Genoa, Italy; and the Division of Rheumatology, Cincinnati Children's Hospital and Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA.

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C.A. Wallace, MD, Associate Professor, Division of Immunology and Rheumatology, Children's Hospital and Regional Medical Center, Department of Pediatrics, University of Washington School of Medicine; N. Ruperto, MD, MPH, Senior Scientist, Pediatric Rheumatology InterNational Trials Organization, IRCCS G. Gaslini, Pediatria II; E.H. Giannini, MSc, DrPH, Professor, Division of Rheumatology, Cincinnati Children's Hospital and Medical Center, University of Cincinnati College of Medicine.

Address reprint requests to Dr. C.A. Wallace, Department of Rheumatology, Children's Hospital and Regional Medical Center, 4800 Sandpoint Way NE, Seattle, WA, 98105, USA.
E-mail: cwallace@u.washington.edu

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are also needed to define various stages of disease quiescence that are demarcated by duration of disease quiescence and whether or not the patient is receiving anti-arthritis medications. Each of these stages should have prognostic value, ideally expressed as the probability of disease recurrence during a defined time period.

We began by determining if such criteria were in existence by searching the literature for uses of the term remission. The term is used extensively, but inconsistently, in publications of JIA therapy and outcome. Among 24 papers published in 2000-2001 describing juvenile rheumatoid arthritis (JRA, the term used in North America to define certain categories of JIA) and remission, only 3 used the same definition of remission. Thus, it is evident that no uniform, validated criteria for defining quiescent disease (or its recognizable stages) are in widespread use.

Our effort was limited to the development of clinical criteria that can be applied in the day-to-day clinic setting, rather than attempting criteria for biological disease arrest that would require complex assays of inflammatory mediators and/or sophisticated imaging studies. Criteria for 3 stages of disease quiescence were defined: inactive disease, clinical remission on medication, and clinical remission off medication. Our chief goal was to begin the process of establishing a common vocabulary for use by clinicians, researchers, regulatory agencies, and drug developers to describe the same clinical conditions, the importance of which has recently been described[16,17].

MATERIALS AND METHODS

The project was conducted using well-established consensus formation methodology designed to combine ideas and judgments from a large group of experts. The methodologies used were the Delphi Questionnaire approach and Nominal Group Technique (NGT)[18]. The former utilizes a series of increasingly focused questionnaires to gather and refine opinions of experts in the field. NGT involves a structured face-to-face meeting designed to allow interactive interchange of opinions to facilitate reaching consensus on the topic of interest. These techniques have been used successfully in rheumatic diseases for the development of response and outcome criteria for JRA, adult RA, adult and childhood SLE, and idiopathic inflammatory myopathies[19-22].

Development of preliminary criteria. Phase 1: Delphi questionnaires. Using the Delphi Technique, 2 sequential questionnaires were sent to 96 senior clinically active pediatric rheumatologists selected from the memberships of the Pediatric Rheumatology Collaborative Study Group (PRCSG), the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Pediatric Section of the American College of Rheumatology (ACR), and the Rheumatology Section of the American Academy of Pediatrics (AAP), and to 150 pediatric rheumatologists from the membership of the Pediatric Rheumatology International Trials Organization (PRINTO). The first questionnaire was open-ended and asked for signs and symptoms that should be considered when determining whether a patient with JIA has achieved clinical remission. For each item listed, the criterion that had to be met was to be specified [i.e., rash, absent; erythrocyte sedimentation rate (ESR), normal]. The questionnaire also asked how long a patient had to be off all anti-arthritis medications in order to be considered in clinical remission off medication. The final question asked the respondent to write his or her own definition of clinical remission.

Items listed by > 80% of respondents were considered to have consensus for inclusion in a definition for clinical remission of JIA. Those items mentioned by > 10% of responders but < 80%, formed the basis of the second questionnaire. The second questionnaire contained 8 yes/no questions aimed at clarifying responses on the initial questionnaire, and 3 open-ended questions.

Phase 2: Consensus conference. Following the surveys, a 2-day consensus conference was held in May 2003. The meeting was attended by 20 senior pediatric rheumatologists from the memberships of PRINTO, CARRA, and the PRCSG. Nine countries were represented. Prior to the meeting participants were sent a syllabus of relevant articles and plans for the meeting in order to facilitate pre-conference research and thought formation. The goal of the meeting was to reach consensus on preliminary criteria for inactive disease, and clinical remission of JIA, both on and off medications. During the NGT sessions, attendees were asked first to work individually and then express their opinions in a controlled, guided discussion. On the second day, the group met to review and refine the results from day 1, to decide on final preliminary criteria for inactive disease and clinical remission on and off medications, to decide what clinical remission off medications should predict, and to discuss plans for validation.

Statistical analysis. Analyses of the questionnaires and the consensus exercises were descriptive in nature.

RESULTS

Phase 1: Delphi questionnaires. Response rate to the first questionnaire was 55% (83/150) among PRINTO members and 49% (47/96) from the membership of the PRCSG, CARRA, the Pediatric Section of the ACR, and the Rheumatology Section of the AAP representing 34 countries. Four criteria for inclusion in a definition of clinical remission achieved consensus from Questionnaire 1. These criteria included the absence of swollen joints, fever, or rash (attributable to active arthritis), and a normal ESR. Questionnaire 2 resulted in consensus on 5 additional items including absence of serositis, active uveitis, and abnormal ESR or CRP (due to active arthritis). Joints with limited range of motion could be present if completely explained by prior damage considered irreversible and not due to currently active arthritis. Joint tenderness could also be present if not accompanied by swelling, pain on motion, or limitation of motion.

Phase 2: Consensus conference. Criteria/items upon which no consensus was reached by the Delphi questionnaires and items needing further clarification formed the basis for the NGT conference. Twenty-two problems were addressed and consensus (> 80% agreement) was reached on 17 (Table 1).

The state of inactive disease and 2 types of clinical remission were developed: clinical remission on medications and clinical remission off medications. Figure 1 shows a representation of the possible phases. The group felt that a patient must exhibit a degree of durability of the inactive disease state prior to declaring either form of clinical remission achieved. Inactive disease on medication must persist for a minimum of 6 months before clinical remission on medication is achieved. Similarly, the patient must maintain inactive disease for a minimum of 12 months after discontinuation of all antiinflammatory, antirheumatic, and anti-uveitis medications prior to being classified in a state of clinical remission off medication.

Table 1. Preliminary criteria for inactive disease and clinical remission of JIA.

Inactive disease:
No joints with active arthritis[a,b]
No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA
No active uveitis (to be defined)
Normal ESR or CRP (if both are tested, both must be normal)
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.
Clinical remission on medication. The criteria for inactive disease must be met for a minimum of 6 continuous months while the patient is on medication in order for the patient to be considered to be in a state of clinical remission on medication.
Clinical remission off medication. The criteria for inactive disease must be met for a minimum of 12 continuous months while off all anti-arthritis and anti-uveitis medications in order for the patient to be considered to be in a state of clinical remission off medication.

[a]The ACR defines a joint with active arthritis as a joint with swelling not due to bony enlargement or, if no swelling is present, limitation of motion accompanied by either pain on motion and/or tenderness. [b]An 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 non-rheumatological reasons such as trauma.

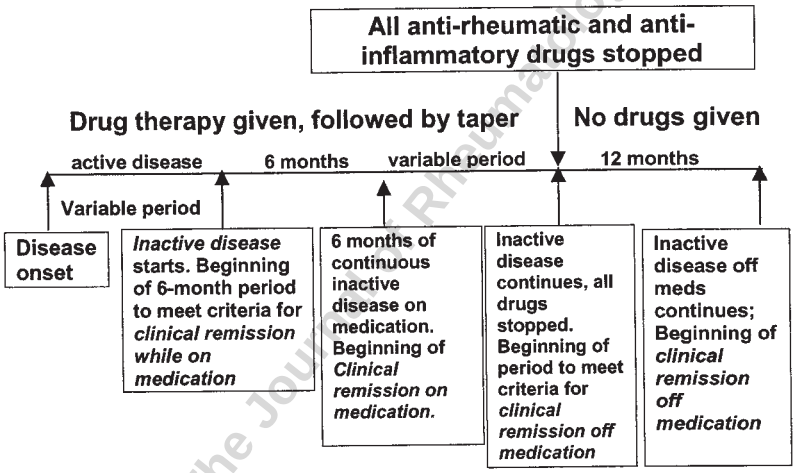

Figure 1. Time periods and events from disease onset to clinical remission off medication.

The group agreed that the criteria needed to be predictive of some probability of future disease recurrence determined by evidence-based validation. Table 2 shows the ranking of the desired predictive ability of these (or future) criteria for clinical remission off medications.

It was acknowledged that JIA represents several categories of disease not addressed in this project, and that later efforts should work towards criteria for clinical remission for all JIA.

Unresolved assessments. The consensus conference participants identified the presence or absence of uveitis as an important item to be included in the criteria. However, all agreed that pediatric rheumatologists are not the proper subspecialists to determine criteria for inactive uveitis. Several ophthalmologists with prominent expertise in uveitis were consulted prior to the meeting. There was a lack of consensus about criteria for inactive uveitis among them. As an example, one uveitis expert felt that the presence of 1-5 cells (i.e., 1+ score) in the anterior chamber of the eye was consistent with inactive uveitis, while another was adamant that no cells should be present. Standardization of criteria for inactive uveitis has begun through the efforts of the National Eye Institute and the American Uveitis Society. Until a definition is available, pediatric rheumatologists must rely upon the definition of inactive uveitis used by each individual ophthalmologist treating their patients, with the realization that there may be substantial variability in the meaning of the term.

Other items that may be important to include in a definition of inactive JIA, but that did not achieve consensus are the presence of rheumatoid nodules, hepatomegaly, and morning stiffness. If morning stiffness is to be included, a decision will have to be made as to its maximum duration. These items are presented here with the intent that they will be included in

Table 2. What clinical remission off medication should predict (in order of preference by conference attendees).

Sum of Ranks	Chance of Disease Flare/Relapse
65	< 20% in the next 5 years
58	< 10% in the next 2 years
46	< 10% in the next 5 years
35	< 25% in the next 5 years
27	< 5% in the next 2 years
14	< 20% in the next 1 year
11	< 40% in the next 5 years
8	< 5% in the next 5 years
8	< 50% in the next 2 years
4	< 50% in the next 1, 5 years

validation processes to determine if they increase the sensitivity, specificity, or other performance characteristics of the criteria.

DISCUSSION

An internationally agreed upon, validated, operational definition of remission applicable to JIA is needed for a variety of clinical and scientific agendas.

New medications and new therapeutic regimens using innovative combinations of drugs have begun to show the potential to induce extended periods of complete disease quiescence in children with JIA. Future studies of these therapeutic approaches will require standardized criteria for clinical remission to assess treatment effects in JIA and compare results across studies.

Regulatory agencies allow pharmaceutical manufacturers to seek a claim of complete clinical response (clinical remission while on medication) and remission for anti-rheumatic agents. As an example, the US Food and Drug Administration Guidance for Industry Document entitled Clinical Development Programs for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis contains criteria for clinical remission for adult rheumatoid arthritis (RA) modified from Pinals, *et al*[23]. The criteria for remission for JIA in this guidance document were not developed systematically and are not widely accepted. This is evidenced by the non-standardized use of the term in published investigations. Well-validated, internationally agreed upon criteria specifically designed for children with JIA will be needed in future studies aimed at obtaining the remission claims.

Pharmacogenetics and pharmacogenomics will likely have a major impact on the ability of clinicians to choose an appropriate medication treatment plan to induce remission of JIA. Criteria for remission are of paramount importance in order to correctly phenotype patients for responsiveness to therapeutic agents.

These preliminary criteria for inactive disease and clinical remission of JIA were developed using Delphi and NGT consensus formation techniques with participation from pediatric rheumatologists worldwide. Criteria were sought for use by the clinician in day-to-day practice, the clinical investigator evaluating new therapies, and the basic scientist studying disease processes in need of clinically phenotyping the patient. Our proposed criteria include measures of disease activity that can be easily performed in clinical practice. One of the overriding themes of this project was to avoid inclusion of variables that are not readily assessable in either the clinic or routine laboratory, and that are not likely part of standard care.

These draft criteria are a work-in-progress and undoubtedly will go through considerable iteration. As more insight is gained into the pathogenesis of childhood arthritis, and the factors promoting persistent disease are understood, this knowledge will add to an improved definition of perhaps biologic remission.

Meaning of remission. Conference participants unanimously agreed that any definition of clinical remission should have prognostic implications. The adult criteria developed by Pinals, *et al*[23] allowed patients to be either on or off medications with no evidence of disease for 2 months. Any time period aimed at denoting permanence of the inactive disease state will be arbitrary unless it can be shown through clinical evidence what the likelihood of disease recurrence is among those who have managed to meet the criteria. While rheumatologists recognize that clinical remission off medication does not imply a cure, the achievement of such a state should mean something in terms of prognosis in order to be useful to the patient/parent and clinician. Thus, varying degrees of predictive ability of the term clinical remission off medication were discussed and ranked during the conference. It should be noted that these predictions of future disease flare are expressed as probabilities for a period of time and cannot be absolute.

Validity. The preliminary criteria have face validity (the extent to which an instrument or criteria appear valid to those who are using it) and the variables included are certainly capable of change (responsiveness) during the 6 to 12 months during which durability of response will be investigated. With forthcoming decisions about the inclusion of morning stiffness, rheumatoid nodules, and hepatomegaly, content (comprehensive) validity should also be attained. As a work-in-progress, the criteria must be examined for predictive, criterion (accuracy), and discriminant validity, all of which serve to estimate the overall construct validity [agreement between a theoretical concept (remission) and an instrument or procedure to measure it]. Existing databases will be used initially to test the criteria for their validity in defining each disease state (retrospective validation) and this must be followed by prospective validation. Future efforts will be needed to address the issues of psoriatic arthritis and enthesitis related arthritis as well as the category of other arthritis in order to develop a more comprehensive definition of clinical remission that encompasses all of JIA.

In summary, we are presenting these preliminary criteria as the first step of a work-in-progress. Their development has included input from pediatric rheumatologists worldwide.

Finalized criteria will be designed for easy use in day-to-day practice, in clinical trials of therapies, in investigations of outcome, and by basic scientists studying disease mechanisms. Above all, it is hoped that these criteria will be used and refined so that the term clinical remission of JIA can have a clearly understood meaning for our patients.

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