Optimisation of disease assessments in juvenile idiopathic arthritis

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ABSTRACT

A variety of clinical measures are available for assessment of disease status of children with juvenile idiopathic arthritis (JIA) in clinical trials, clinical care and long-term outcome surveys. The American College of Rheumatology (ACR) Pediatric 30 remains the preferred primary outcome measure for registrative trials, although in most therapeutic studies performed in the 2000s patients were also evaluated for more stringent levels of improvement, that is, applying the ACR Pediatric 50, 70, 90, and 100 response criteria. Because the recent therapeutic advances have made inactive disease an achievable goal in most patients, it has been suggested that endpoints for future clinical trials incorporate the evaluation of disease activity state, namely the assessment of inactive disease and low disease activity. The introduction of the Juvenile Arthritis Disease Activity Score (JADAS) and the establishment of its cut-offs for various disease activity states may foster the implementation of the treat-to-target strategy in both clinical trials and routine practice. In recent years, there has been an increased focus on the inclusion of patient and child perspectives in health outcome measures through the use of parent/child-reported outcomes. Integration of these measures in the clinical evaluation is considered important as they reflect the parent's and child's perception of the disease course and effectiveness of therapeutic interventions. Future studies will show whether the newer imaging modalities, namely magnetic resonance imaging and ultrasound, can replace conventional radiography for the assessment of structural joint damage and its progression.

Introduction

Until the early 1980s, there were virtually no standardised measures for the assessment of the disease status of children with juvenile idiopathic arthritis (JIA). An important advance took place in 1982, when Giannini and Brewer (1, 2) published the guidelines for the clinical assessment of children with chronic arthritis enrolled in therapeutic studies of anti-inflammatory and anti-rheumatic medications made by the Pediatric Rheumatology Collaborative Study Group. Over the following 3 decades, there has been an intense effort to develop and validate additional standardised outcome measures for JIA, including measures of disease activity and disease damage, criteria for assessment of therapeutic response, and questionnaires for the evaluation of physical functioning and health-related quality of life (HRQL) (reviewed in 3-5).

The tools that are currently available for the disease assessment of children with JIA in clinical trials, clinical care and long-term outcome studies, which are shown in Table I, are the subject of this review.

Clinical trials

The primary outcome measure for the assessment of response to therapy in JIA clinical trials is represented by the so-called American College of Rheumatology (ACR) Pediatric 30 criteria (6). These criteria are based on a 6-variable core set, which includes the physician global rating of overall disease activity (physician global), the parent/patient global rating of overall well-being (parent/patient global), the assessment of physical functional ability, the count of joints with active arthritis, the count of joints with restricted motion, and an acute-phase reactant. A patient is classified as responder in a clinical trial if he/she shows an improvement of at least 30% from baseline in at least 3 of any 6 core set variables, with no more than 1 of the remaining variables worsening by more than 30%. Disease flare

Table I. Juvenile idiopathic arthritis outcome measures for disease assessment in clinical trials, clinical care and long-term databases.

Clinical trials
ACR Pediatric response criteria
Criteria for disease activity states (*e.g.* inactive disease, low disease activity)
JADAS cut-offs
JADAS response criteria
Clinical care
Physician-reported outcomes
Parent/patient-reported outcomes
Acute phase reactants
cJADAS
Long-term databases
Physician-reported outcomes
Parent/patient-reported outcomes
Physician-centered outcomes
Parent-centered outcomes
JADI
Radiographic scoring systems

ACR: American College of Rheumatology; JADAS: Juvenile Arthritis Disease Activity Score; cJADAS: clinical JADAS; JADI: Juvenile Arthritis Damage Index.

is defined as worsening of two variables by ≥40% without improvement in more than one variable by ≥30% (7).

Because a 30% improvement in outcome variables is no longer considered sufficient to establish the effectiveness of a therapeutic intervention (8), in most clinical trials performed in the 2000s patients were also evaluated for more stringent levels of improvement, that is, applying the ACR Pediatric 50, 70, 90, and 100 response criteria (9-15). Recently, the ACR Pediatric 30 was adapted for use in clinical trials in systemic JIA, by adding the demonstration of the absence of spiking fever (≤38°C) during the week preceding the evaluation (14, 15).

It has been argued that because the ACR Pediatric criteria emphasise a change in disease state, they do not permit the measurement of patients' actual disease activity at the end of a clinical trial (8). This limitation is relevant in the light of the recent advances in the management of JIA, which have moved the therapeutic goals increasingly toward the attainment of a state of inactive disease or, at least, of low disease activity (16-18). To overcome this shortcoming, it has been suggested that future clinical trials incorporate, beside the assessment of the ACR Pediatric response, the evaluation of the disease activity state (8).

In recent years, several measures of disease activity state in JIA have been developed. The criteria for inactive disease and clinical remission for JIA are the most popular of such measures (16, 19). Based on these criteria, a patient is classified as having inactive disease at a specific point in time when he or she has no joints with active disease, no systemic manifestations attributable to JIA, no active uveitis, normal values of acute-phase reactants, a physician global assessment of disease activity indicating no disease activity, and a duration of morning stiffness of ≤15 minutes. When the above criteria are met for a minimum of 6 consecutive months while the patient is receiving anti-rheumatic medications or for a minimum of 12 consecutive months after the patient has discontinued all anti-rheumatic medications, a patient is classified as being in the state of clinical remission with medication or without medication, respectively (19).

The definition of inactive disease requires the total absence of signs and symptoms of disease activity and is, therefore, very strict. However, achievement of true inactive disease remains difficult in many patients, particularly those with polyarticular or systemic JIA. It has been proposed that a more attainable goal, particularly in the short time frame of a clinical trial, could be a state of low disease activity, which is an intermediate state between high disease activity and remission, though very close to remission (20, 21). The state of low (or minimal) disease activity in JIA has been defined as the presence of a physician global ≤3.4, a parent/patient global ≤2.5, and a swollen joint count of ≤1 in polyarthritis, and as the presence of a physician global ≤2.5 and a swollen joint count of 0 in oligoarthritis (20).

In 2009, the first composite disease activity score for JIA, named the Juvenile Arthritis Disease Activity Score (JADAS), was published (22). This tool includes the following 4 variables: 1) physician global; 2) parent/patient global; 3) count of joints with active arthritis, assessed in 71 (JADAS71), 27 (JADAS27), or 10 (JADAS10) joints; and 4) ESR, normalised to a 0–10 scale. The JADAS is calculated as the arithmetic sum of the scores of its 4 components, which yields a global score of 0–101, 0–57, and 0–40 for JADAS71, JADAS27, and JADAS10, respectively. A JADAS version including the C-reactive protein (CRP) level instead of the ESR was found to perform similarly to the original format (23).

The cut-off values of the JADAS corresponding to the states of inactive disease and low, moderate and high disease activity, or reflecting the physician, parent, or child subjective rating of remission, or the parent or child satisfaction with the outcome of the illness were recently established (24-27). The JADAS cut-offs represent qualified therapeutic targets for clinical trials and may support decisions about patient enrolment. Furthermore, they are ideally suited to implement a treat-to-target strategy aimed to achieve and maintain tight disease control, with treatment escalation if a target score is not reached or is lost (28).

Recently, Horneff and Becker defined the improvement thresholds for the JADAS10 (29). Once validated in an independent cohort of JIA patients, these thresholds will represent a worthy addition to the ACR Pediatric response criteria in future clinical trials.

Clinical care

Outcome measures used in JIA clinical care include physician-reported outcomes, parent/child-reported outcomes (PCROs), and acute phase reactants (usually ESR and CRP). The traditional physician-reported outcomes are the physician global and the count of joints with swelling, tenderness/pain on motion, restricted motion, and active disease (1, 30). A joint with active disease is defined as a joint with swelling or, if swelling is not present or detectable clinically (as in the case of the cervical spine or hip), with tenderness/pain on motion and restricted motion (31).

A number of tools for the assessment of PCROs in JIA are available, including VAS for rating of child's well-being and intensity of pain, and question-

naires for the measurement of physical functioning and health-related quality of life (HRQOL) (3-5, 32, 33). There are, however, several PCROs not addressed by conventional instruments, such as evaluation of morning stiffness and overall level of disease activity, rating of disease status and course, proxy- or self-assessment of joint involvement and extra-articular symptoms, description of side effects of medications, and assessment of therapeutic compliance and satisfaction with the outcome of the illness, which may provide valuable insights into the influence of the disease and its treatment on child's health. This consideration have provided the rationale for the development of multidimensional questionnaires for the assessment of patients with JIA in standard clinical care that integrate all main PCROs (34).

The latest advances in the areas of PCROs in childhood arthritis include the definition of the symptom threshold beyond which children or their parents consider the disease status as satisfactory (35), and the development and validation of composite disease assessment indices entirely based on PCROs (36).

It has been suggested that the use of a three-variable version of the JADAS, which does not include the acute phase reactant, may increase the feasibility of the tool for use in daily practice. Indeed, inflammatory markers frequently are not obtained or available during a visit, particularly in children who are not receiving medications and, thus, do not require laboratory monitoring, or in children with persistent oligoarticular JIA, who generally do not undergo laboratory assessment (37). This simplified version of the JADAS, which we have proposed to name clinical JADAS (cJADAS) (38), was found to correlate closely with the original version and to possess a comparable construct validity (37). The cut-offs of the cJADAS corresponding to the states of inactive disease and low, moderate and high disease activity were recently defined and validated (38).

As shown in Figure 1, regular application of the JADAS or cJADAS as well as of the composite disease assessment indices based on PCROs in day-to-day care enables plotting their longitudinal scores in a graph to provide an overview of the patient's course over time (see also ref. 39).

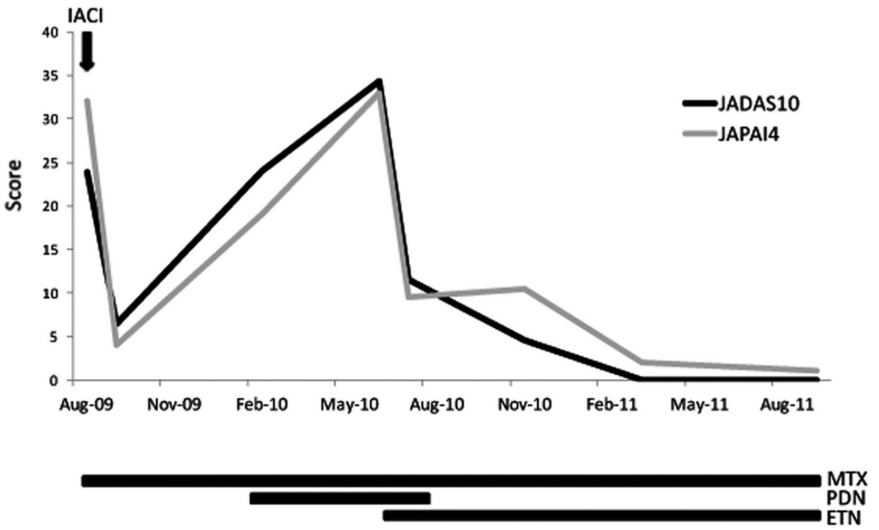

Fig. 1. Time course of composite scores, along with therapeutic interventions, in a patient with juvenile idiopathic arthritis. JADAS: Juvenile Arthritis Disease Activity Score; JAPAI: Juvenile Arthritis Parent Assessment Index; IACI: intraarticular corticosteroid injection; MTX: methotrexate; PDN: prednisone; ETN: etanercept.
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Long-term databases

Most of the clinical measures mentioned above are also included in long-term outcome surveys. Instruments that are specifically suited for use in such studies are those that are aimed to assess disease damage. Damage in JIA may be related to prolonged synovial inflammation, which may lead to permanent alterations in joint structures. Permanent changes may also develop in extra-articular organ/systems (*e.g.* the eye, as a result of uncontrolled iridocyclitis) or result from adverse effects of medications.

The Juvenile Arthritis Damage Index (JADI) is a clinical tool that reflects the overall biological outcome of JIA (40). It comprises two parts: one devoted to the assessment of articular damage (JADI-A) and the other devoted to the assessment of extra-articular damage (JADI-E). In the JADI-A, 36 joints or joint groups are assessed for the presence of damage and the damage observed in each joint is scored on a three-point scale (0 = no damage; 1 = partial damage; 2 = severe damage, ankylosis, or prosthesis). The maximum total score is 72. The JADI-E includes 13 items in five different organs/systems. Each item is scored as 0 or 1 if damage is absent or present, respectively. Due to the relevant impact of ocular damage on the child's health, in each eye a score of 2 is given in case the patient has had ocular surgery and a score of 3 in case the patient has developed legal blindness. The maximum total score is 17.

Another important method for assessment of disease severity and course is represented by the evaluation of radiographic joint damage and its progression. In recent years, there has been a great deal of effort to devise new radiographic scoring systems or validate existing methods for use in JIA. Some of these measures have undergone a thorough validation process and have proved to be reliable and valid for assessment of radiographic progression in children with chronic arthritis (reviewed in 41).

There is nowadays a growing interest in the use of new imaging modalities, such as magnetic resonance imaging (MRI) and ultrasound, in children with JIA (42, 43). These techniques have been shown to be more sensitive in disclosing early erosive changes in adult patients with rheumatoid arthritis (44, 45). However, although these tech-

niques are promising, experience with their use in paediatric patients is still limited. Thus, they are unlikely to replace plain radiography as the standard for evaluating joint damage in JIA for some time to come.

Among PCROs, the most relevant data for inclusion in long-term databases are those obtained from the assessment of physical functioning and HRQL. Multidimensional questionnaires are also well suited to collect long-term data as they enable keeping a flow sheet of patient's course over time. A flow sheet may facilitate the recognition of possible changes in clinical symptoms, functional capacity, pain, overall well-being, fatigue, and psychological status from previous visits (46).

Conclusion

In the last 3 decades, a number of clinical measures for disease assessment of children with JIA in clinical trials, clinical care and long-term outcome studies have been developed and validated. Although the ACR Pediatric 30 remains the preferred primary outcome measure for registrative trials in JIA, considering that current clinical practice also mandates good overall disease control, it would be desirable that future clinical trials incorporate, among secondary end points, the evaluation of disease activity state (*e.g.* the assessment of inactive disease and low disease activity, and JADAS cut-off values). The establishment of the cut-offs of the JADAS and cJADAS for various disease activity states may foster the implementation of the treat-to-target strategy in both clinical trials and routine practice. In recent years, there has been an increased focus on the inclusion of patient and child perspectives in health outcome measures through the use of PCROs. Integration of these measures in the clinical evaluation is considered important as they reflect the parent's and child's perception of the disease status and course. Future studies will show whether the newer imaging modalities, namely MRI and ultrasound, can replace conventional radiography for the assessment of structural joint damage and its progression in children with chronic arthritis.

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