
Toward a treat-to-target approach in the management of juvenile idiopathic arthritis

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Received and accepted on September 20, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S157-S162.

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Key words: juvenile idiopathic arthritis, treat-to-target, remission, inactive disease, minimal disease activity, acceptable symptom state

ABSTRACT

Recent advances in the management of juvenile idiopathic arthritis (JIA) render disease remission an attainable goal in many, if not most, patients. This has led to suggestions that future treatment guidelines include an overriding goal to achieve clinical remission or, at least, minimal disease activity. Furthermore, implementation of treatment strategies aimed at achieving and maintaining tight disease control in standard paediatric rheumatology practice has been proposed. A compelling argument is available at this time to suggest that the incorporation of treat-to-target approach in the management of children with JIA may improve disease outcome. Recently, descriptions of disease states that represent suitable therapeutic targets, such as inactive disease, minimal disease activity, or parent- or child-acceptable symptom states, have been developed. In addition, criteria for these states based on the Juvenile Arthritis Disease Activity Score (JADAS) have been identified. Future studies will clarify whether the addition of an imaging assessment to the management of children with JIA will improve the prediction of clinical outcomes.

Introduction

Juvenile idiopathic arthritis (JIA) is an umbrella term that encompasses a heterogeneous group of disorders characterised by prolonged synovial inflammation that may cause destructive damage to joint structures (1). Permanent changes may also develop in extraarticular organs, particularly the eye (as a complication of chronic anterior uveitis), or may result from side effects of medications (2). The morbidity of disease and treatments can lead to serious impairment of physical function and have a marked impact on the quality of life of children and their families (3, 4).

The management of JIA has changed dramatically over the past two decades, owing to the shift towards early aggressive interventions and the development of new therapeutic agents including methotrexate and biological medications, and combination treatment strategies (5-7). This progress has increased the potential to achieve disease remission or, at least, minimal levels of disease activity, and has consequently moved the therapeutic aims increasingly towards the attainment of an inactive disease status (8-14). Complete disease quiescence is regarded as the ideal therapeutic target because its achievement helps in prevention of further joint damage and disability, and may enhance physical function and quality of life (15). Notably, in the present review the use of the term “minimal disease activity” is as identical to “low disease activity” for the adult rheumatology community.

Studies in adults with rheumatoid arthritis (RA) have shown that patient outcomes are improved if a practice to aim for minimal levels of disease activity by frequent adjustment of therapy according to quantitative indices is implemented (16-18). Although a similar approach has not yet been reported in JIA, the achievement of the state of inactive disease at least once in the first 5 years was found to be associated with lower levels of long-term damage and lower functional impairment in children with polyarthritis (15). In addition, a greater magnitude of clinical response in the first 6 months of methotrexate therapy was found to predict a more favourable long-term outcome (19). Conversely, the time spent in the state of active disease in the first 2 years was the most significant factor associated with the duration of active disease over the following years (20). However, a rational approach to the management of JIA is hampered by the inability to predict the long-term outcome early in

Competing interests: none declared.

the course of illness (21). Until now, reports concerning achieving disease remission with present treatment of JIA are scarce. Inactive disease has seldom been included as a primary endpoint in randomised controlled trials of disease-modifying anti-rheumatic drugs or biologic medications in JIA. Recently, a preliminary definition of inactive disease in JIA (8, 9) has been used as primary outcome measure in a randomised, double-blind, placebo-controlled trial of two aggressive treatment strategies in children with early JIA (22). However, there is the need to obtain information about the potential of currently used medications to induce clinical remission in the real world of standard clinical practice. In adult RA, the strategy of tight control, aiming for remission, appears more important than the agent (23). The European League Against Rheumatism recommendations for the management of RA, reinforced by the treat-to-target approach (24), have set remission as the primary treatment goal in everyday clinical practice (25). Recently, the British Society for Paediatric and Adolescent Rheumatology (BSPAR) has promulgated the Standards of Care for children and young people with JIA (26) and the American College of Rheumatology (ACR) has issued a set of recommendations for the treatment of JIA (27). However, neither the BSPAR Standards of Care nor the ACR recommendations have clearly formulated a goal of achievement of inactive disease. Considering that disease remission is now attainable for many, if not most, patients with JIA, it has been suggested that future management guidelines should include as overriding goal the achievement of clinical remission or, at least, minimal disease activity (28, 29). This objective would ideally be coupled with implementation of the concept of targeting at remission in paediatric rheumatology settings. The incorporation of the treat-to-target strategy in clinical practice requires the availability of validated and clinically useful criteria that describe accurately the clinical states of remission or near-remission. Furthermore, the optimal treatment target(s) should be clearly defined.

Table I. American College of Rheumatology provisional criteria for defining inactive disease in oligoarticular (persistent and extended), polyarticular (rheumatoid factor-positive and negative), and systemic juvenile idiopathic arthritis*.

Inactive disease:

- No joints with active arthritis[‡]
- No fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA
- No active uveitis as defined by the SUN Working Group[§]
- ESR and CRP level within normal limits in the laboratory where tested or, if elevated, not attributable to JIA
- Physician's global assessment of disease activity score of best possible on the scale used
- Duration of morning stiffness of ≤ 15 minutes

*All criteria must be met. JIA: juvenile idiopathic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

[‡]A joint with active arthritis is defined 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 or tenderness.

[§]The Standardisation of Uveitis Nomenclature (SUN) Working Group defines inactive anterior uveitis as "grade zero cells", indicating <1 cell in field sizes of 1 mm by a 1-mm slit beam.

Adapted with permission from reference 9.

Criteria for inactive disease and clinical remission

Preliminary criteria for inactive disease and clinical remission on medication for JIA were developed in the early 2000s through an international collaborative effort (8). Based on these criteria, a patient is classified as having inactive disease at a specific point in time when he/she has no joints with active disease, no systemic manifestations attributable to JIA, no active uveitis, normal values of acute phase reactants, and a physician global assessment of disease activity indicating no disease activity. When the criteria for inactive disease are met for a minimum of 6 consecutive months while the patient is receiving anti-rheumatic medications, the patient is classified as being in the state of clinical remission with medication. When the criteria for inactive disease are met for a minimum of 12 consecutive months after the patient has discontinued all anti-rheumatic medications, the patient is classified as being in the state of clinical remission without medication. Recently, the criteria have been modified by providing a specific definition for uveitis and abnormal erythrocyte sedimentation rate and by adding the duration of morning stiffness of ≤ 15 minutes (9) (Table I).

Definition of minimal disease activity

The definition of inactive disease requires the total absence of signs and symptoms of disease activity and is,

therefore, very stringent. However, achievement of true inactive disease either in routine practice or in clinical trials remains problematic in many patients, particularly those with polyarticular or systemic JIA. Furthermore, the state of inactive disease is often not maintained over long periods (10).

It has been proposed that in standard clinical care a more attainable goal could be to induce and maintain at least a state of minimal disease activity, which is an intermediate state between high disease activity and remission, though very close to remission (12). In adult patients with RA, this state is deemed to be a useful target of treatment by both the physician and the patient, given current treatment possibility and limitations (30). The state of minimal disease activity in JIA has been described as the presence of a physician's global rating of disease activity ≤ 3.4 , a parent's global rating of well-being ≤ 2.5 , and a swollen joint count ≤ 1 in polyarthritis, and as the presence of a physician's global assessment of disease activity ≤ 2.5 and a swollen joint count = 0 in oligoarthritis (12).

Parent- and child-acceptable symptom state

It has been argued that criteria for inactive disease are based only on physician-reported outcomes and an acute phase reactant, whereas parent proxy-reported and child self-reported outcomes are neglected (31). A parent

global assessment is included in minimal disease activity criteria for polyarthritis, but not for oligoarthritis. Hence, both clinical inactive disease and minimal disease activity definitions may not reflect adequately the parent and child perception of the disease status.

A goal to analyse whether a therapeutic intervention leads to an acceptable state according to the parent or the child has led to proposal of the concept of parent/child acceptable symptom state in JIA (31). This state has been defined as the symptom threshold beyond which the child health status is considered as satisfactory by the parent or the child. The cut-off values for parent-reported, child-reported and physician-reported outcome measures, and acute phase reactants that defined the acceptable symptom state for parents and children have been estimated using both the 75th percentile method and receiver-operating-characteristic curve analysis (31). The cut-off values for children were lower than those for parents, suggesting that children may request a more stringent disease control to feel satisfied. Cut-offs were higher in systemic arthritis than in the other JIA categories, reflecting the greater burden of disease in the systemic subset.

JADAS cut-offs for remission, minimal disease activity and acceptable symptom state

An alternative approach to the measurement of disease activity is based on composite disease activity scores, such as the Disease Activity Score (DAS) (32) and the Clinical Disease Activity Index (CDAI) (33) in adult RA. These tools are aimed to quantify the absolute level of disease activity by providing one summary number on a continuous scale. Recently, the first composite disease activity score for JIA, termed Juvenile Arthritis Disease Activity Score (JADAS), has been reported (34). The JADAS includes the following 4 variables: 1) physician global rating of overall disease activity, measured on a 0–10 cm visual analogue scale (VAS); 2) parent/child ratings of well-being, measured on a 0–10 cm VAS; 3) count of active joints, assessed in 71 (JADAS71), 27 (JADAS27) or 10

Table II. JADAS cut-off values for JIA disease states*

Disease state	All JIA	Oligoarthritis	Polyarthritis
Inactive disease	1	1	1
Physician-assessed remission	2	2	2
Parent-assessed remission	2.3	2.3	2.3
Child-assessed remission	2.2	2.2	2.2
Minimal disease activity	–	2	3.8
Parent acceptable symptom state	4.7	3.2/3.5 [§]	5.2/5.4 [§]
Child acceptable symptom state	4	3	4.3/4.5 [§]

*Cut-off values apply to all versions of the Juvenile Arthritis Disease Activity Score (JADAS) versions, unless otherwise indicated. JIA: juvenile idiopathic arthritis.

[§]Cut-off value for JADAS-27/cut-off value for JADAS-10 and JADAS-71.

Adapted with permission from reference 36.

(JADAS10) joints; 4) erythrocyte sedimentation rate (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.

Recently, a JADAS version including the C-reactive protein instead of the ESR was found to perform similarly to the original format (35). The JADAS provides simple and intuitive reference values that can be used to monitor the disease course over time in an individual patient or to compare the disease status across single patients or patient groups. It is, therefore suited for use in clinical decision making, particularly to implement a treat-to-target approach aimed to achieve and maintain tight disease control, with treatment escalation if a target JADAS score is not reached.

The use of the JADAS as a guide to pursuing tight disease control requires cut-off values to identify the target states of remission or minimal disease activity. Recently, cut-off values of the JADAS that corresponded with inactive disease and minimal disease activity, or reflected the physician, parent or child subjective rating of remission or the parent or child satisfaction with the outcome of the illness were established (Table II). These cut-offs proved to have capacity to predict disease outcome (36).

The feasibility of the JADAS for use in standard clinical practice might be enhanced, by analogy with CDAI versus DAS in adult RA (37), by establishment of a 3-item version, which does not include the acute phase reactant. Inflam-

matory markers frequently are not obtained or available at a visit. Therefore, physicians often do not have laboratory results available during the clinical evaluation. The lack of this information would hinder the potential to make immediate therapeutic decisions based on the JADAS and, thus, the potential benefit of intensifying therapy.

Imaging and remission

In adult patients with RA, there is evidence that synovitis detected by imaging may be frequent in patients who meet clinically-defined remission criteria, and is associated with adverse clinical, functional, and structural outcomes (38). This observation has raised a plea to aim for remission defined by imaging (39). Recent studies in children with JIA have also shown that remission defined by clinical criteria does not always equate to the complete absence of inflammation as measured by new sensitive imaging techniques, such as MRI and ultrasound.

Tzaribachev *et al.* (40) reported a high frequency of MRI-detected synovitis in patients with clinically inactive disease. It is unknown whether this finding involves a risk of silent progression of damage and whether it should affect the physician's decision to discontinue treatment. However, subtle changes revealed by MRI in clinically unaffected joints have been found to predict extension of arthritis in children with recent-onset oligoarthritis (41).

A high prevalence of ultrasound-detected subclinical synovitis was found in joints that were recorded as normal on clinical examination (42–45).

Furthermore, evidence of ongoing synovial pathology in one or more joints was observed in a sizable proportion of patients classified as having inactive disease on clinical grounds (46, 47). However, the clinical significance and prognostic value of these findings is unclear, as the presence of abnormalities on ultrasound, including power Doppler signal, did not predict subsequent synovitis flare (47). This finding contrasts with the observation in adults with RA that vascularisation detected by power Doppler ultrasound predicts short-term disease flare after clinical remission (48-49).

The lack of predictive value of power Doppler signal in JIA has been related to the difficulty to establish whether the presence of juxta-articular flow at power Doppler examination in the growing child represents normal flow of the well-vascularised cartilage of the epiphysis or synovial hyperemia indicating inflammation. Another possible explanation lies in the potential confounding influence of the physiologically enhanced synovial blood flow on the appraisal of low-grade power Doppler signal in growing children (47, 51, 52).

What is the optimal target of therapy in JIA?

Nowadays it is widely agreed that the primary target for the treatment of JIA should be a state of clinical remission. Clearly, when remission is interpreted as the complete absence of any measurable sign of disease activity, the definition of inactive disease is most stringent. However, achievement (and maintenance) of true inactive disease is still problematic in routine clinical practice in many children with JIA, particularly among those with the most severe forms (10). Furthermore, the stringency of inactive disease criteria may lead to miss some instances that are deemed as remission by the attending physician, but do not meet the criteria. We found that only 70% of the episodes in which the physician had judged subjectively the disease state as remission met the inactive disease criteria (Bracciolini *et al.*, unpublished observation). This phenomenon is partially due to the physician not always providing a global

rating of 0 (which is requirement of the criteria) in the presence of disease remission. Some recent therapeutic studies have modified the inactive disease criteria to set the minimum score of the physician global rating at 1 or even 2 (53-55), which is indirect evidence that the physician does not always provide a global rating of 0 in the presence of disease remission.

It has been suggested that in standard clinical care a more attainable goal could be to induce and maintain at least a state of minimal disease activity (12). The definition of minimal disease activity in JIA is less stringent than that of inactive disease. For instance, it allows the physician global assessment to be up to 2.5 in oligoarthritis and up to 3.4 in polyarthritis. In the aforementioned study of the agreement between subjective and objective definitions of remission and minimal disease activity (Bracciolini *et al.*, unpublished observation), the minimal disease activity criteria were met in 87% of the instances that were judged subjectively as disease remission by the physician. This finding suggests that the state of minimal disease activity is closer to the physician perception of clinical remission than the state of inactive disease. However, although minimal disease activity constitutes a useful target for treatment over the short-to-intermediate term, the achievement and maintenance of true inactive disease should be the ultimate goal in every child with JIA.

Another important target for disease management is the parent- and child-acceptable symptom state. Although the definition for such state is less strict than that of both inactive disease and minimal disease activity, incorporation of a therapeutic target that reflects parent and child assessment ensures that the level of disease activity reached with the therapeutic intervention is satisfactory for parents and children.

Whichever disease state is selected as therapeutic target, the application of the JADAS constitutes an easy and flexible method to guide therapeutic interventions aimed to pursue tight disease control. In adult patients with RA, a treat-to-target approach with treatment escalation if goal DAS was not reached, led

to a significantly better status compared to traditional therapeutic strategies in articular, functional, and radiographic outcomes (16, 17). Clinical trials based on the treat-to-target approach are desirable in children with JIA, in order to determine whether the implementation of disease activity score-driven strategy in clinical practice influences key outcomes.

There is currently a growing interest in the use of imaging for the assessment of disease remission in JIA (13, 51, 52). Among the imaging modalities used to detect synovial inflammation, ultrasound is more practical than MRI, as it can be applied in the clinic and is suited for frequent applications. Furthermore, it enables scanning multiple joints at one time and does not require sedation in younger children.

However, although recent studies have shown evidence of ongoing synovial pathology on ultrasound in a sizable proportion of children with JIA classified as having inactive disease on clinical grounds (46, 47), the clinical significance of these findings remains unclear. Indeed, the presence of abnormalities on US, including power Doppler signal, did not predict subsequent synovitis flare (47). This finding suggests that residual synovitis on imaging should not affect clinical decisions and, in particular, should not indicate treatment in the absence of clinical indications. More data are needed to establish the value of imaging in the definition of remission in children with JIA.

Conclusion

There is now a compelling argument to suggest that the incorporation of a treat-to-target approach in the management of children with JIA may improve disease outcomes. In recent years, definitions for the states of clinical remission and minimal disease activity, and for the parent- and child-acceptable symptom state have been developed. Furthermore, criteria for these states based on the JADAS have been identified. All these tools constitute suitable targets to implement therapeutic strategies aimed at tight disease control in paediatric rheumatology settings. Future studies will clarify whether the

addition of an imaging assessment to the management of children with JIA will improve the prediction of clinical outcomes. Furthermore, further investigations will establish whether targeting therapy to imaging measures provides better outcomes compared to treating to clinical targets alone. It is anticipated that the treat-to-target approach aimed at clinical or imaging remission in JIA will constitute a major area for research in paediatric rheumatology in the coming years.

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