Recent developments in disease activity indices and outcome measures for juvenile idiopathic arthritis

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Abstract

There has been a concerted and important international effort to develop and validate disease activity and outcome instruments specific to JIA in recent years. This review aims to describe the disease assessment indices important to routine clinical care and integral to the design of outcome studies and clinical trials in JIA. In view of the increasing number of JIA clinical studies and clinical trials, together with a number of national and international paediatric biologic registers, it is important that knowledge of these new outcome measures is widespread, such that results can be placed in a meaningful context.

Key words: disease activity, outcome measures, juvenile idiopathic arthritis, epidemiology, paediatric/juvenile rheumatology, JADAS, standards of care.

Introduction

Inflammatory arthritis occurs in approximately 10:100 000 children each year [1], with the majority subsequently diagnosed with JIA. JIA is a diagnosis of exclusion, an idiopathic inflammatory arthritis lasting 6 weeks or more, beginning before the 16th birthday.

JIA is an umbrella term summarizing the internationally recognized classification system for chronic paediatric arthritides. Developed in 1993 by the Paediatric Standing Committee of the ILAR and revised in 2001, the classification presents eight mutually exclusive subtypes of JIA [2, 3]. The goal of these criteria is to facilitate clinical care and research into this complex, multisystem disorder. Marked heterogeneity characterizes the differences between ILAR JIA subtypes and even within individual ILAR subtypes; an increasingly recognized clinical heterogeneity in disease patterns between children reflects probable variability in disease pathogenesis.

Assessment tools of chronic illness can be divided into two broad categories: measures of disease activity and disease damage. In JIA, disease activity refers to the overall level of potentially modifiable intra- and extra-articular inflammatory disease at a particular point in time. Important measures of disease damage include joint damage and long-term disability, with their associated economic implications. Valid and reliable measures of disease activity and damage facilitate communication in the clinical setting and standardize research studies. Historically, multiple single measures have been employed in JIA, but the heterogeneous nature of JIA and normal developmental changes of childhood and adolescence ensure that no single measure can reliably capture overall disease activity or outcomes in all children with JIA.

Composite disease activity scores enable the integration of several different domains of disease activity and outcome into one single numerical value and are more precise than their individual components, potentially increasing the statistical power of clinical trials [4]. They improve the consistency of patient care across different clinical settings and help patients better understand their own disease activity [5]. A number of clinical trials in RA have confirmed the benefits of treating to predefined composite targets with respect to improved outcomes and reduced radiological progression [6–8], where changes to therapy are made in response to predefined levels of disease activity using composite outcome measures.

The advent of new biologic treatment agents and the growing evidence base for the treatment of JIA have
resulted in a paradigm shift in the management of JIA, with an emphasis on the prevention of damage and normalization of functional outcomes [9]. Treating to target in JIA is likely to improve clinical outcomes still further, but requires valid and feasible disease activity and outcome measures to provide measurable evidence of what many clinicians are already attempting in the clinical care of individual patients. Disease assessment tools designed for adult populations are not necessarily valid, reliable or accessible to the paediatric population. Patterns of joint involvement encountered in JIA may be different from adult inflammatory arthritides. Certain aspects of adult measures, such as tender joint counts, are not feasible in very young children, who may be unable to localize and report tender joints. The significant reliance on proxy reports in paediatric practice constitutes a further barrier to the simple application of adult indices.

JIA is not a disease confined to childhood, with more than one-third of children continuing to have episodes of active inflammation during their adult years [10, 11]. No composite disease activity score or outcome measure has been validated for use in adults with JIA, although the juvenile arthritis disease activity score (JADAS) has been employed as a summary of disease activity in adults with JIA [12]. Although disease assessment tools designed for adult populations may be more appropriate in adult life than childhood, assessment tools such as the RA DAS and the BASDAI may not be an effective measure of overall disease activity in adults with JIA. Moreover, the employment of tools designed for other inflammatory illnesses may contribute to the continued confusion about JIA in adult practice. Following transfer of care, adult physicians must engage with the importance of applying appropriate disease activity and outcome assessment tools to adults with JIA.

This review aims to describe recent international developments in the assessment of disease activity and damage/disability in JIA, both within the context of routine clinical practice and in clinical trials. It comprises a summary and discussion of the JIA core outcome variables and the JIA composite measures currently available: measures of improvement, current disease status and patient- or parent-centred outcomes.

**JIA core outcome variables**

Early clinical trials in JIA employed a range of single disease activity and damage measures [13]. Over time, some study end points were shown to be redundant and some unreliable with poor reducibility [14, 15]. The lack of standardization in the reporting of clinical trials made it difficult to compare results across different studies. In response to these concerns, a core set of outcome variables were developed for JIA (Table 1) [16]. The variables were identified through formal item generation and reduction processes [17] and multiple studies have confirmed the validity of the criteria [16, 18]. Individual variables are discussed in more detail below.

**Physician global assessment of disease activity**

The physician global assessment of disease activity (PhysGA) of overall disease activity is a subjective interpretation of the patient’s overall status measured on a horizontal 10 cm visual analogue scale (VAS). The relatively simple scoring system reflects a complicated set of internal judgements on every aspect of the patient’s condition. The PhysGA responds strongly to increases in disease activity [19] and, although subjective, is widely regarded as a reliable measure of disease activity. Correlation of the PhysGA with joint counts and pain assessment varies between ILAR subtypes of JIA [20], probably reflecting differences in disease patterns between the ILAR subtypes.

**Patient/parent general evaluation of overall well-being**

The patient/parent general evaluation (ParGE) employs a validated 10 cm VAS to determine the child’s/family’s assessment of overall well-being. The ParGE is equally subjective, varying with age, general health and emotional well-being. Wide variations in patterns of normal development affect the age at which a child can understand the VAS. Self-assessment of subjective symptoms cannot be expected from preschool children so the parental opinion must be sought as a proxy. It is difficult to be sure how accurately proxy assessments reflect the child’s perception of his/her own well-being. A recent comparison of proxy and adolescent assessments of disability, pain and well-being reported moderate agreement overall, with a higher likelihood of discordance in those with severe disease or a shorter duration of illness. The presence of depressive symptoms in the child or young person has also been shown to predict disagreement between adolescents and their proxy [21].

**Active and restricted joint counts**

Both active and restricted joint counts reflect clinically important changes in health status, although the active joint count (AJC) is more responsive to disease flare than the limited joint count (LJC) [19]. However, the term AJC is not always clearly defined and is not used consistently between studies. The range of a single joint can improve, but such subtle changes cannot be identified by simple yes/no scoring systems. Such limitations mean that joint counts alone cannot be routinely regarded as reliable, reproducible surrogates for disease activity.

**Erythrocyte sedimentation rate**

Acute phase reactants (APRs) are objective measures of inflammation. The ESR is moderately responsive to disease flares, while other APRs (including the CRP, white blood cell and platelet counts) exhibit a very limited response [19]. APRs are non-specific and may increase with intercurrent illness. Perhaps as a consequence, correlation with joint counts and global scores in children with systemic onset oligoarticular and polyarticular JIA is poor [22].
### Table 1: Strengths and weaknesses of disease activity and outcome measures developed for JIA

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<tr>
<th>Disease activity or outcome measure</th>
<th>Definition</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tr>
<td><strong>JIA core outcome variables [16]</strong></td>
<td>Physician global assessment of disease activity (PhysGA) (100 mm VAS) Patient/parent global assessment of well-being (ParGE) (100 mm VAS) Active joint count Limited joint count Acute phase reactant (ESR) Function (CHAQ)</td>
<td>Extensive validation studies have confirmed the feasibility and validity of the core outcome variables [16, 18]. Individual variables are accessible and straightforward to assess.</td>
<td>Requires assessment of all six variables at a single time point, potentially time consuming. The ESR may not always be available in the routine clinical setting. The AJC is not always clearly defined. Physician and parent global scores are subjective and parental proxy reports may not reflect the child’s own perceptions. Cannot be used to assess change in disease activity over time.</td>
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<td><strong>JIA definition of improvement [16]</strong></td>
<td>ACR Pedi30: three of any six of the core set criteria improved by at least 30% with no more than one worsening by &gt;30% ACR Pedi50: three of any six of the core set criteria improved by at least 50% with no more than one worsening by &gt;30% ACR Pedi70: three of any six of the core set criteria improved by at least 70% with no more than one worsening by &gt;30%</td>
<td>High sensitivity, specificity and face validity. Allows the standardized assessment of changes in disease activity over time, an important outcome in interventional trials. Allows comparison of study results.</td>
<td>Cannot be used to define an individual patient’s disease status at a single point in time. Cannot be used to compare one patient with another. Not easy for patients and families to understand. A definition including levels of improvement (e.g. low, moderate, high) may be more meaningful in the clinical setting.</td>
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<td><strong>JIA definition of disease flare [30]</strong></td>
<td>A number of definitions have been developed and validated. The definition most commonly employed in clinical trials involving children with polyarticular pattern disease is as follows: Three of any six of the core set criteria worsening by at least 30% with no more than one improving by &gt;30%. Contingencies: If either the active joint count or limited joint count are included, there must be at least a 2 joint increase. If either the physician or parent global scales are included, there must be at least a 2 cm worsening (on a 0–10 cm scale). For systemic-onset JIA: fever spikes &gt;38 °C for at least 2 of the preceding 7 days not due to infection</td>
<td>Integral to the innovative design of randomized double-blind controlled withdrawal trials, allowing all children access to the trial drug from point of entry to trial.</td>
<td>Definitions for minor and major flare could help criterion become more clinically useful. May benefit from further modification by ILAR subtype.</td>
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<td><strong>ACR criteria for clinically inactive disease (CID) in oligoarticular, polyarticular and systemic-onset JIA [36]</strong></td>
<td>No joints with active arthritis&lt;br&gt;No fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA&lt;br&gt;No active uveitis as defined by the SUN working group&lt;br&gt;ESR/CRP within normal limits in the laboratory where tested or, if elevated, not attributable to JIA&lt;br&gt;PhysGA best possible on scale used&lt;br&gt;Duration of morning stiffness ≤ 15 min&lt;br&gt;All criteria must be met</td>
<td>Integral to improving standardization of reporting of remission in JIA.&lt;br&gt;Allow remission to be employed as an end point in JIA clinical trials.</td>
<td>Validation studies used clinical trial datasets including only children with polyarticular course JIA without systemic features or uveitis and excluding children with psoriatic and enthesitis-related JIA. As yet, there is no definition of clinically inactive disease in children with these ILAR subtypes.&lt;br&gt;Parent proxy-reported and child-reported outcomes are not represented equitably.&lt;br&gt;Duration of morning stiffness can be difficult to determine in very young children or children with additional needs.&lt;br&gt;It is not yet clear whether achievement of remission correlates with improved function/quality of life or the prevention of further joint damage.</td>
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<td><strong>Criteria for inactive disease and clinical remission [35]</strong></td>
<td>On medication: criteria for inactive disease met for at least 6 consecutive months on medication&lt;br&gt;Off medication: criteria for inactive disease met for at least 12 consecutive months off medication</td>
<td>Good clinical applicability. Helps children and their families understand changes to treatment regimes.</td>
<td>As above, validation studies used clinical trial datasets including only children with polyarticular course JIA. This definition may be less valid in children with systemic-onset, oligoarticular, psoriatic and enthesitis-related JIA.&lt;br&gt;As above, parent proxy-reported and child-reported outcomes are not represented equitably.</td>
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<td><strong>Definition of minimal disease activity [39]</strong></td>
<td>Oligoarticular JIA: PhysGA ≤ 2.5 cm and no swollen joints&lt;br&gt;Polyarticular JIA: PGA ≤ 3.4 cm, PGE ≤ 2.1 cm, maximum of one swollen joint</td>
<td>A useful concept in routine clinical practice and epidemiological research.</td>
<td>Extra-articular features of JIA are not included in the assessment&lt;br&gt;The validity of the criteria for all ILAR subtypes of JIA remains unclear.&lt;br&gt;May require further modification in response to evolving treatment regimes and associated expectations for outcome.&lt;br&gt;Parental/patient understanding of the definition of MDA not yet known.</td>
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<td><strong>The Juvenile Arthritis Disease Activity Score (JADAS) [43]</strong></td>
<td>Linear sum of four components:&lt;br&gt;(i) PhysGA: 0–10 cm VAS&lt;br&gt;(ii) ParGE: 0–10 cm VAS&lt;br&gt;(iii) Active joint count assessed in one of three ways:&lt;br&gt;( \text{JADAS-10: any involved joint up to a maximum of 10} )&lt;br&gt;( \text{JADAS-27: 27 joints including cervical spine, elbows, wrists, first to third metacarpophalangeal, proximal interphalangeal, hips, knees and ankles} )&lt;br&gt;( \text{JADAS-71: all 71 joints} )&lt;br&gt;(iv) ESR: Normalized on a 0–10 scale using the formula below to avoid excessive weight in the overall index: ( \frac{\text{ESR (mm/h) – 20}}{10} )</td>
<td>Good construct and discriminant validity with good responsiveness to change.&lt;br&gt;Allows comparison of current disease activity or responsiveness between two patients or two groups of patients.&lt;br&gt;Has the potential to standardize care across different clinical settings.</td>
<td>Further validation studies are indicated to ascertain the validity of JADAS in the clinical setting. Extra-articular features such as systemic features and uveitis are not captured by this index.</td>
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<td>JADAS response criteria for JIA [47]</td>
<td>Oligoarticular disease course: ID = 1, MDA = 2 Polyarticular disease course: ID = 1, MDA = 3.8</td>
<td>Aids interpretation of JADAS scores. May be used to monitor the disease course over time, enabling tighter disease control and treating to target. Internationally agreed reference values may simplify clinical trial entry or response criteria. May help children and families understand the need for changes to the therapeutic regime.</td>
<td>The validity of the cut-offs in children with extra-articular features (systemic features or uveitis) is unknown. It is currently unclear how well the cut-off values correlate with remission defined by laboratory indices or radiological investigations. Further validation studies are required.</td>
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<td>The Juvenile Arthritis Parent Assessment Index and the Juvenile Arthritis Child Assessment Index [49]</td>
<td>Parent or child global assessment of overall well-being (Par GE, 10 cm VAS) Parent/child rating of pain intensity (10 cm VAS) Assessment of physical function (CHAQ or Juvenile Arthritis Functionality Scale) Assessment of health-related quality of life (CHQ or Paediatric Rheumatology Quality of Life scale) JAPAI-4/JACAI-4 includes all four items JAPAI-3/JACAI-3 exclude the HRQOL assessment</td>
<td>Good construct and discriminant validity, good to moderate responsiveness to clinically important change. May improve the understanding of the impact of JIA on the child and family. May improve the effectiveness of clinical care.</td>
<td>Further validation studies in different patient populations are indicated. May increase the complexity and duration of clinical encounters.</td>
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<td>Parent acceptable symptom state in juvenile arthritis (JA-PASS) [51]</td>
<td>Examples of cut-off values for all ILAR subtypes of JIA include: JA-PASS: AJC = 1, PhysGA 1.1, ParGE 2, ESR 22 JA-CASS: AJC = 1, PhysGE 1, ParGA 1.2, ESR 21</td>
<td>May help physicians and research teams determine whether an observed change is acceptable to the patient.</td>
<td>Although they may be clinically useful, these tools are unlikely to represent future treatment targets as both JA-PASS and JA-CASS cut-offs appear to correspond to a higher level of disease activity than MDA.</td>
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<td>Child acceptable symptom state in juvenile arthritis (JA-CASS)</td>
<td>Examples of cut-off values for all ILAR subtypes of JIA include: JA-PASS: AJC = 1, PhysGA 1.1, ParGE 2, ESR 22 JA-CASS: AJC = 1, PhysGE 1, ParGA 1.2, ESR 21</td>
<td>May help physicians explain clinical decisions to children and their families.</td>
<td>The effect of normal development on the child’s comprehension of disease activity remains unclear.</td>
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Functional ability
Although disability may not reflect current disease activity in a child with long-standing JIA, the accurate evaluation of disability is central to the assessment of disease damage. Moderate to severe disability at initial presentation is the strongest predictor of disability at 1 year [23]. The Childhood Arthritis Assessment Questionnaire (CHAQ) measures function in the context of an individual child’s current physical well-being and is a reliable and valid tool in JIA [24], although sometimes time consuming for families. The CHAQ can take up to 10 min to complete [25], although shorter completion times are commonly reported [26]. It is difficult to be sure how accurately the CHAQ reflects an individual child’s function. Comorbid conditions, in particular chronic idiopathic pain syndromes, can impair the reliability of the CHAQ. Parental CHAQ reports can disagree significantly with the level of disability observed by staff in the clinical setting, with the level of disagreement increasing with severity of arthritis and the parental perception of pain [27]. Although the CHAQ should reflect the child’s average performance over the preceding week, not necessarily apparent to clinical staff at a single visit, functional assessments are subjective in nature. There is a wide variation in levels of agreement between adolescent and parental proxy reports of function [28]. Wherever possible, the self-reporting of CHAQ questionnaires should be encouraged.

CHAQ reflects current disease activity more accurately earlier in the disease course, for similar reasons to the LJC [29]. Inclusion of the CHAQ in the core outcome variables (COVs) may also impede their ability to describe changes in disease activity over time.

Composite disease measures in JIA
Although the COVs remain the gold standard assessment tool for therapeutic response in clinical trials, a rapidly increasing number of composite indices of disease activity and damage have been developed specifically for JIA in the past few years. The indices outlined below are central to modern clinical trial design and are increasingly relevant to routine clinical care.

Composite measures of improvement in JIA clinical trials
The definition of improvement in JIA
The JIA definition of improvement (Table 1) published in 1997 uses the COVs to describe changes in disease activity over time, an important outcome in interventional trials [16]. The definition can be applied to all ILAR subtypes of JIA, although children with systemic-onset JIA are additionally required to report the absence of fever >38°C during the preceding week.

The minimum level of improvement reported as a primary outcome in JIA clinical trials (the ACR paediatric 30 response criteria) requires at least 30% improvement from baseline in three of the six COVs with no more than one of the six deteriorating by >30% [16]. As the care of children with JIA has advanced [9], the minimum acceptable level of improvement has increased accordingly. More significant levels of improvement at the 50%, 70%, 90% and even 100% level (ACR Pedi50, Pedi70, Pedi90 and Pedi100, respectively), previously reported as secondary outcomes, are now employed as outcome measures in interventional trials.

The widespread introduction of the definition of improvement has standardized the reporting of clinical trials, enabling comparison with previous and future studies. Although these definitions are pragmatically useful in clinical trials, they cannot be used to define an individual patient’s disease status at a single point in time, so may not be immediately meaningful or useful to families in the routine clinical setting.

Definition of disease flare
A number of definitions of disease flare have been analysed for JIA [30]. The preliminary flare definition recommended in 2002 requires worsening in any two of the six COVs by at least 40% without concomitant improvement of more than one of the remaining COVs by at least 30% [30]. The definition of flare commonly employed in clinical trials involving patients with polyarticular pattern disease requires worsening of at least 30% from baseline in three of the six COVs with no more than one improving by >30% (Table 1) [31–33].

The definition of disease flare is central to withdrawal-flare study designs, often employed in JIA trials to date, which allow open-label treatment with the experimental drug for all children, followed by the double-blind randomization of withdrawal among responders [34], employing disease worsening or flare as an endpoint. As our expectations for outcomes in JIA continue to improve, more stringent definitions of disease flare will become relevant in the context of clinical trials. Inclusion of other parameters including the presence of enthesitis or uveitis where appropriate, or specific biomarkers of disease activity in certain ILAR subtypes, may all improve the applicability of this definition to the clinical setting.

Composite measures of current disease status
A number of internationally agreed definitions of disease status in JIA aim to simplify the monitoring of disease activity over time and inform changes to the therapeutic regime. Such definitions have the potential to improve the quality of care provided at a single centre or across a number of different clinical settings.

Definition of inactive disease and clinical remission
In 2004 an international consensus group developed preliminary criteria for inactive disease and clinical remission for persistent oligoarticular, RF positive, RF negative and systemic-onset JIA (Table 1) [35]. Prospective validation studies resulted in further modification of the definition of active uveitis (Standardisation of Uveitis Nomenclature Working Group definition), abnormal ESR/CRP and the
addition of a sixth criterion, duration of morning stiffness $\geq 15$ min [36]. The criteria have been employed in a number of clinical studies and clinical trials [37, 38].

These criteria for inactive disease include a number of variables excluded from the COVs. The criteria are the first of the composite indices to acknowledge the importance of uveitis as a marker of active inflammatory disease, although the yes/no requirement is rather insensitive. The duration of morning stiffness is difficult to ascertain in very young children (particularly if not walking independently), so it may not always be available. Equally, the stress and difficulty associated with regular blood monitoring in children means that the ESR/CRP may not always be available in routine practice. Furthermore, the exclusion of parent/child-reported indices may compromise overall validity.

**Definition of minimal disease activity**

Despite recent advances in therapies, achievement of complete clinical remission remains challenging. Minimal disease activity (MDA) can be a more realistic initial goal than remission. A preliminary definition of MDA in oligoarticular and polyarticular course JIA was validated in 2008 (Table 1) [39]. A robust definition of MDA may represent a useful treatment target for researchers and clinicians, with the potential to improve overall outcomes. However, limited patient numbers in the original validation study, together with the exclusion of a number of extra-articular features, may impair the validity of the definition in certain ILAR subtypes. Furthermore, the definition was derived in the pre-biologic era and may require updating. Since physicians, parents and children frequently disagree in the assessment of disease activity measures [27, 40–42], the exclusion of the ParGE from the MDA definition for oligoarticular course JIA may compromise its validity.

**The juvenile arthritis disease activity score**

The juvenile arthritis disease activity score (JADAS) is a composite disease activity score specific to JIA, comprising the sum of four clinically derived variables (AJC, PhysGA, ParGE and ESR) (Table 1) [43]. Published in 2009, JADAS measures actual disease activity at a single point in time and allows the comparison of the response of one patient/group of patients with another. Three versions of JADAS have been developed, each employing one of three active joint counts (71-, 27- and 10-joint counts). The range of the composite disease activity score is 0–40 for JADAS-10, 0–57 for JADAS-27 and 0–101 for JADAS-71.

The LJC and functional assessment become less responsive to changes in disease activity as damage accumulates [29]. Exclusion of the LJC and functional assessment allows JADAS to describe disease activity at any point in the disease course. Validation studies have shown the correlation of JADAS with swollen and tender joint counts, parental pain assessment, CHAQ and CRP to be moderate to high [43]. JADAS discriminates well between ACR Pedi 30, 50 and 70 with good responsiveness to change. Correlations of the Disease Activity Score 28 (DAS28) and the Clinical Disease Activity Index (CDAI) with the same indices in adults with RA are generally lower. A potential limitation of the JADAS may relate again to the heterogeneity of JIA. The majority of patients in the original validation studies were clinical trial patients, with a predominance of polyarticular course disease [43, 44]. Two population-based studies of JADAS have been published. The first, in 2012, reported a close correlation between JADAS-CRP and JADAS-ESR [45]. The second, in 2013, proposed exclusion of the ESR (the JADAS-3) to improve clinical applicability [46]. Further validation studies will help to confirm the validity of JADAS in the clinical setting for all ILAR subtypes of JIA.

JADAS cut-offs corresponding to remission, MDA and acceptable symptom state (a subjective rating of remission or satisfaction with disease outcome by the physician, parent or child) were published in 2012 (Table 1) [47]. The JADAS cut-off corresponding to inactive disease was the lowest (1 for all children). The JADAS score corresponding to a state of MDA may be more useful in routine clinical practice (and was set at 2 for children with oligoarticular and 3.8 for children with polyarticular disease patterns). The applicability of these data to children with extra-articular features of JIA remains unclear to date.

**Patient- or parent-centred composite measures in JIA**

Physicians, parents and children frequently disagree in the assessment of disease activity [27, 40–42], implying that there are aspects of the disease and its treatment that cannot be captured by clinicians or researchers. Patient-reported outcome measures (PROMs) provide detailed insight from the patient and/or family of the impact of the disease and its treatment on the overall well-being and quality of life of the child. PROMs are important outcomes in clinical studies and clinical trials, with the potential to improve the evaluation of routine clinical care pathways.

However, a number of important challenges exist in developing PROMs. Measurement tools and data collection techniques must be valid, reliable and practical in the context of routine clinical care or busy clinical trial schedules. For PROMs to be used effectively in clinical studies and clinical trials, study cohorts must be representative of the whole population.

**The Juvenile Arthritis Multidimensional Assessment Report**

The Juvenile Arthritis Multidimensional Assessment Report (JAMAR) is a disease activity and disability assessment, published in 2011, intended for use in conjunction with physician-derived indices [48]. The questionnaire includes 15 patient-centred items addressing well-being, pain, function, health-related quality of life, morning stiffness, disease activity, disease status, joint and extra-
articular disease, compliance, side effects and overall satisfaction with illness outcome. It has been shown to be valid and feasible in the clinical setting, although the English-language version awaits formal validation studies. JAMAR is the first paediatric measurement tool to include a patient/parental proxy assessment of joint symptoms.

Parent- and child-centred composite disease assessment indices

The Juvenile Arthritis Parent Assessment Index (JAPAI) and Juvenile Arthritis Child Assessment Index (JACAI) are parent-centred and child-centred composite outcome scores including four clinically derived variables (ParGE, a functional assessment, parental pain VAS and a health-related quality of life assessment) (Table 1) [49]. Initial validation studies are reassuring, but further validation is indicated in different patient populations. Such composite indices will increase the complexity and duration of clinical encounters, so validity and clinical effectiveness must be clearly proved before incorporation into routine practice.

The parent and child acceptable symptom state

As the treatment of JIA continues to improve, it is increasingly important to define and achieve a symptom state acceptable to the physician, parent and child. The patient acceptable symptom state (PASS) is a relatively new concept in rheumatology, defined as the symptom threshold beyond which rheumatology patients consider themselves to be well [50]. The definition of a paediatric acceptable symptom state has the potential to help clinicians and research teams understand whether an observed change is acceptable to the child and/or parent.

The validity of the acceptable symptom state concept in JIA was examined in 2012 (Table 1) [51]. Cut-off values corresponding to a satisfactory symptom state [the parent acceptable symptom state in juvenile arthritis (JA-PASS) and the child acceptable symptom state in juvenile arthritis (JA-CASS)] were defined for a number of outcome measures, including the COVs. Overall, threshold levels for JA-CASS were lower than for JA-PASS, suggesting that children may require tighter disease control than their parents anticipate. The absence of active joints strongly predicted both JA-PASS and JA-CASS. Due to the relative infrequency of such diagnoses, the study sample included relatively few patients with enthesitis-related or psoriatic JIA. Developmentally and socially important differences in the ability of children and their parents to understand disease states may impact on the validity of this work. Consequently the availability and effectiveness of appropriate education programmes is of paramount importance to the success of these modern assessment tools.

JADAS cut-off values corresponding to JA-PASS (4.7 for all JIA) and JA-CASS (4 for all JIA) have recently been published [47]. As in adult practice [52], the PASS cut-offs are higher than the cut-off values associated with MDA or inactive disease [47].

Quality of life as an outcome measure

Overall health status and quality of life can be severely affected in children with JIA, particularly children with significant pain or functional impairment [53]. Health-related quality of life (HRQOL) is therefore an important outcome measure and a number of different assessment tools exist. Examples include the Child Health Questionnaire (CHQ) [54], Paediatric Quality of Life Inventory (PedsQL) Rheumatology Module 3.0 [55] and Juvenile Arthritis Quality of Life Questionnaire (JAQQ) [56].

HRQOL assessments can be time consuming and parental-proxy reports must be interpreted with care [57]. A novel web-based patient-reported application system was published in 2013 [58]. Modern electronic tools have the potential to revolutionize the systematic assessment and discussion of HRQOL issues in the clinical setting.

Summary and future work

Accurate assessment of disease activity and damage in JIA remains complex. The development of composite assessment tools allows clinicians and investigators to incorporate important extra-articular manifestations in these scores. The 1997 ACR definition of improvement is simple for both researchers and clinicians to use [16]. However, capturing maintenance of an acceptably low level of disease activity over a prolonged period of time as a more effective way to prevent damage and disability may be more clinically relevant than the decrease from a high level of disease activity documented by the initial definition of improvement [39]. The JADAS, which can quantify disease activity at a single point in time, has significant potential in the context of clinical trials and in routine practice [43]. Validated criteria (cut-off values) identifying different disease activity states (inactive disease, clinical remission and MDA) allow clinicians to interpret and compare JADAS scores in one patient or between patients [47]. In view of the stress and difficulty obtaining regular blood tests in paediatric practice, exclusion of the ESR from JADAS (the JADAS-3) may improve its applicability to routine clinical practice [46].

PROMs have the potential to further refine our understanding of this disease and its treatments. In particular, the JAMAR is an innovative multidimensional assessment tool, capturing patient/parental views on joint symptoms and quality of life, significantly expanding the information obtained from clinical assessment tools [48].

The heterogeneity of JIA remains a barrier to defining response and remission criteria for children across all ILAR subtypes. Many disease activity indices have been developed using clinical trial datasets not necessarily reflecting real-world JIA populations. The disease status indices described may not be valid in all ILAR subtypes and may require further modification by subtype. It is important to note that any new set of measurable criteria requires multiple validation studies, and use can continue
to evolve for many years. Ongoing validation studies are essential if valid and feasible response and remission criteria are to be established for JIA. Any future change in internationally accepted classification criteria for JIA would necessitate a review of all of these measures.

Changes in disease activity reported in clinical trials may not translate directly to an acceptable symptom state for parents and/or children with JIA. Further work is necessary to develop ways to translate clinical trial results into clinically relevant and useful outcomes and develop composite indices of disease activity and damage applicable to routine clinical practice. The application of modern touchscreen technologies may be an innovative solution to the collection of parent-/child-centred outcome measures. Novel imaging technologies and biomarkers may address some of the limitations of the currently available composite measures.

The considerable international efforts to date, engaging with this difficult yet fundamental area of clinical practice, have resulted in high-quality clinical trials, expanding the evidence base for treatment of children with JIA. However, the disease activity and outcome measures outlined here are not all used in routine clinical practice in many centres. It is important that knowledge and integration into routine clinical practice of these new outcome measures be widespread, such that clinical trial results can be placed in a meaningful context.

Further work is needed to address the appropriate use of composite measures in adults with JIA. Composite measures developed specifically for JIA are likely to be useful in adult practice, with the potential to guide drug therapy and improve our understanding of long-term outcomes, and these measures require further validation in this context. Moreover, the widespread introduction of generally accepted quantifiable measures of disease activity and disease damage have the potential to improve patient care through direct comparison of clinical standards of care and better access for all patients to relevant registries, clinical studies and clinical trials.

Rheumatology key messages

- An increasing number of disease activity and damage/disability measures specific to JIA have been developed.
- Knowledge of disease activity measures in JIA should be widespread among researchers and clinicians.
- Quantifiable measures of disease activity and damage/disability may improve standards of clinical care in JIA.

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