

# The Time Has Come to Include Assessment of Radiographic Progression in Juvenile Idiopathic Arthritis Clinical Trials



Juvenile idiopathic arthritis (JIA) is a heterogeneous disease characterized by prolonged synovial inflammation that can ultimately lead to destruction of joints<sup>1</sup>. Because prevention of joint changes is a fundamental goal in the long-term management of chronic arthritis, evaluation of radiographic joint damage has become an important tool for assessment of disease severity and progression in children with JIA. Assessment of structural joint damage is a key outcome endpoint in treatment efficacy studies in patients with chronic arthritis<sup>2</sup>, and is now required by the US Food and Drug Administration as a measure of disease progression in clinical trials of potential disease modifying antirheumatic drugs (DMARD)<sup>3</sup>. Radiographic assessment has been included in several randomized studies of DMARD and, more recently, biological agents, in adult patients with rheumatoid arthritis (RA). However, radiographic progression has never been investigated in clinical trials in JIA, reflecting primarily the lack of established radiographic scoring systems for use in the pediatric age group. Since biological agents have been shown to be effective in JIA as well<sup>4-9</sup>, there is a growing need for a reliable radiographic assessment standard for evaluating the potential of these drugs to prevent structural joint damage in JIA.

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<sup>10-20</sup>. 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 JIA. This has led to suggestions that the time has come to include quantitative measures of radiographic damage in therapeutic trials in JIA<sup>20</sup>.

This discussion will summarize the experience gained so far with the use of radiographic scoring systems in JIA, and address the questions that underlie their application in JIA clinical trials.

## DO PATIENTS WITH JIA DEVELOP STRUCTURAL JOINT DAMAGE?

Although it is commonly believed that JIA has a lesser destructive potential than adult RA, several studies have shown that many children with chronic arthritis experience

significant radiographic joint damage<sup>14,15,21-24</sup>. Further, a higher than expected percentage of these patients have been found to have joint space narrowing (JSN) and erosions early in their illness<sup>23-25</sup>. Radiographic changes are seen most frequently in patients who have a polyarticular course of JIA<sup>21,26,27</sup>. In daily clinical practice, patients with polyarthritis are generally candidates to receive early aggressive therapy. The presence of polyarthritis is a prerequisite for a patient's inclusion in controlled trials of second-line or biologic agents<sup>4-6,28,29</sup>. Joint destruction is much less common in children with persistent oligoarthritis, which represents the most benign subset of JIA. This group of patients has been found to have the greatest likelihood to achieve the state of clinical remission without medication along the disease course<sup>30</sup>.

## WHAT ARE THE PROBLEMS WITH THE ASSESSMENT OF RADIOGRAPHIC PROGRESSION IN PEDIATRIC PATIENTS?

It is often said that the assessment of JSN and erosions, which are the main components of the radiographic scoring methods used in adult RA, may not be feasible in pediatric patients with chronic arthritis. In contrast to adults, it is difficult to reliably determine cartilage loss and erosions in children by simple examination of radiographs because growing joints change anatomically over time<sup>31</sup>. To give an example, as bone formation occurs through the ossification of growth cartilage, the width of intercarpal joint spaces varies with age (i.e., width normally decreases with increasing skeletal maturity). This makes evaluation of the degree of JSN challenging in growing children, particularly when joint involvement is symmetric. Evaluation of carpal size may also be confusing when asymmetry in ossification exists because of advancement of maturation secondary to hyperemia or retardation of maturation due to damage<sup>12,32</sup>. Because ossification is incomplete in younger children, significant erosion can occur in the carpus before any change is apparent in the underlying ossification centers. As cartilage ossifies, previous cartilage injury secondary to arthritis may become apparent radiographically. As a result, the

severity of erosion may appear to increase, or at least fail to improve in children whose arthritis is quiescent<sup>12,33</sup>.

Another problem that makes the assessment of radiographic damage in children with arthritis challenging is the development of unique radiographic abnormalities, such as disturbance of bone growth. This phenomenon is the result of inflammation (with the related hyperemia) that occurs in a developing joint and is manifested by acceleration of epiphyseal maturation, premature fusion of epiphyses, and overgrowth or gross deformity of a joint<sup>31,34</sup>. As a result, in younger children with JIA the changes in carpal bones and, to a lesser extent, in distal metacarpal epiphyses frequently manifest as deformity in shape, from squaring to squeezing to gross deformity, rather than as discrete erosions<sup>19,20</sup>. Importantly, an advanced skeletal maturation in the affected side in patients with unilateral wrist disease was found to predict a destructive course of synovitis<sup>32,35</sup>. Thus, due to their frequency and clinical importance, growth abnormalities should be taken into account and graded in a radiographic scoring system for JIA.

The lesser erosive potential of JIA as compared with adult RA and the relatively late occurrence of erosions in pediatric patients can be partly explained by the greater thickness of articular cartilage in growing children. Studies of longterm radiographic progression in JIA have shown that JSN, which reflects the degree of cartilage loss, represents the most common form of radiographic damage throughout the whole disease course<sup>19,20</sup>. Another important aspect that differentiates JIA from adult RA is the better regenerative capacity of articular cartilage of growing children<sup>12</sup>. Studies have shown that children with JIA frequently experience an improvement in radiographic joint damage, which may occur spontaneously or as a result of therapeutic interventions<sup>12,13,19,20,36</sup>.

### WHICH JOINTS ARE BETTER SUITED FOR INCLUSION IN A RADIOGRAPHIC SCORING SYSTEM FOR JIA?

Most scoring methods used in adult patients with RA are based on assessing damage in hand/wrist and, to a lesser extent, foot joints. Damage scored in these joints has been shown to sufficiently reflect damage of large, often weight-bearing joints that are excluded from scoring<sup>37</sup>. It is still unclear whether one or more "index" joints can be identified in JIA. It has been suggested that the wrist joint is particularly suitable for assessing radiographic progression in childhood arthritis. The wrist has been found to be the most vulnerable site of radiographic changes in JIA<sup>22,24-26</sup>. Wrist disease has been associated with a more severe course of arthritis<sup>38,39</sup>, a poorer functional outcome<sup>26</sup>, or a lesser likelihood of short-term therapeutic response<sup>40</sup>. In JIA patients with polyarthritis, wrist disease is frequently associated with involvement of the small joints of the hands. As many as 85% of the 633 patients enrolled in a controlled trial aimed

at comparing intermediate and high doses of methotrexate (MTX) in polyarticular JIA<sup>29</sup> had active disease in the wrist and/or hand joints (Ruperto N, unpublished observation). These findings suggest that the wrist and hand joints represent optimal sites at which to investigate radiographic progression in children with polyarticular JIA.

van Rossum, *et al*<sup>14</sup> evaluated the baseline radiographs of a total of 471 joints/joint groups obtained in 69 children with oligoarticular or polyarticular JIA included in a randomized, placebo-controlled trial of sulfasalazine. They found that the knees, ankles, hands, and feet were the most frequent sites of radiographic changes. Subsequently, these investigators evaluated the baseline to 6-month change in the Dijkstra composite score (see below) in the same patients. Radiographically scored abnormalities were found to change more often in the knees, hands, and feet. This led the authors to propose radiographic assessment of all these joints in future clinical trials, regardless of the presence of signs of arthritis activity<sup>18</sup>.

### WHAT RADIOGRAPHIC SCORING METHODS HAVE BEEN PROPOSED FOR JIA?

Several scoring methods have been developed to measure radiographic damage in JIA. The scores proposed by Pettersson and Rydholm<sup>10</sup> and Dale<sup>11</sup> are semiquantitative in design and enable only a morphological radiographic staging of joint abnormalities on a categorical scale. Although these scores are suitable for investigating the prevalence of qualitative radiographic abnormalities in outcome studies, they are too crude to detect the subtle radiographic changes that generally occur in a clinical trial.

In 1978, Poznanski, *et al*<sup>41</sup> published standards for normal carpal length in growing children, thus enabling a measurement of carpal size that is not dependent on the degree of ossification. This method is based on assessment of the ratio between the radiometacarpal length and the length of the second metacarpal bone. The carpal length reflects a reduction in the joint space in the wrist, rather than erosive damage, and represents, therefore, a good method for identifying cartilage damage in the early phases of joint diseases. The Poznanski score has the advantages of being simple, quick, and reproducible, and it requires little specific training. Availability of standards for normal carpal length is another advantage in studies of growing children. Further, since the radiometacarpal width is not dependent on the degree of ossification of the carpal bones, its measurement helps to overcome the problem of advanced skeletal maturation, which occurs frequently in JIA<sup>31</sup>. However, the Poznanski score is unreliable in cases of advanced carpometacarpal erosions, making it difficult to define the bone ends, and cannot be used once there is radiographic closure of the growth plates of the second metacarpal bone. As well, this method can be applied only to patients with wrist involvement (which accounted for 67% of patients enrolled in the

above noted MTX trial). Notably, normal standards for carpal length were obtained by Poznanski, *et al* on conventional radiographs, which may preclude their comparison with the recent digital images viewed on computing systems.

van Rossum, *et al*<sup>14,18</sup> recently presented the Dijkstra composite score, which assesses the following features as present or absent: soft tissue swelling, osteopenia, JSN, enlargement or other growth disturbances, subchondral bone cysts, and erosions. This score can yield separate values for inflammation, damage, and growth abnormalities. Any increase in the Dijkstra score over time indicates deterioration, whereas any decrease reflects improvement. An advantage of this scoring system is its applicability to all joints. A potential limitation is the lack of grading of changes for severity, which may hamper responsiveness to change over time.

We recently investigated the use of 3 adult scoring systems, the Sharp score, the Larsen score, and the van der Heijde modification of the Sharp score, in assessment of radiographic progression in children with JIA<sup>19,20</sup>. To overcome the difficulties in evaluation of JSN and erosion in growing children, each patient's radiograph was compared with a wrist/hand radiograph obtained in a healthy child of the same sex and bone age. We chose bone age-related instead of chronological age-related or size-related standards because some patients with JIA have advanced skeletal maturation and are small for their age (with their bones being correspondingly small), making these standards unreliable. Comparison of patients' radiographs with printed radiographic standards, such as those published in the *Radiographic Atlas of Skeletal Development of the Hand and Wrist*<sup>42</sup>, is much less accurate than comparison with real standard radiographs. In the largest of these studies, we evaluated the validity of the Sharp/van der Heijde score in 177 children with polyarticular JIA<sup>20</sup>. We believe that the way this method grades bony erosion, which is not only based on the count of the number of erosions but also takes into account their size in relation to bone surface, is particularly suited for application in pediatric patients. Adapted versions of the score were developed through inclusion of 5 new areas for erosion in each wrist, which were found to be frequent sites of erosive changes in patients with JIA. Further, for practical reasons bone deformity (see above) and erosion were considered as equivalent and graded on the same scale. In the investigational settings chosen, the adapted Sharp/van der Heijde score proved quite reliable and showed good construct validity and capability to detect radiographic progression. It should be acknowledged, however, that application of this method in children is complex and requires considerable expertise.

#### **DOES INFORMATION EXIST ON THE USE OF RADIOGRAPHY IN ASSESSMENT OF EFFICACY OF ANTIRHEUMATIC DRUGS IN JIA?**

A few studies, all noncontrolled, have investigated the effi-

cacy of antirheumatic drug therapies on radiographic progression in children with JIA. All used the Poznanski score. Harel, *et al*<sup>12</sup> evaluated serial wrist radiographs in 23 JIA patients with bilateral wrist involvement, before and during MTX therapy. They found that MTX treatment resulted in radiographic improvement in the majority of children who had a clinical response to MTX. Similarly, Ravelli, *et al*<sup>13</sup> reported that after 2 years of MTX therapy in 26 children with JIA, the nonresponders had significantly greater radiographic deterioration than responders. These studies have led to acceptance that MTX has disease modifying potential in JIA.

Recently, the rate of radiographic progression during etanercept therapy was evaluated in 40 children with polyarticular JIA<sup>36</sup>. The median change in Poznanski score between baseline and 1 year in the 40 patients was + 0.3 units, meaning that, on average, patients experienced improvement in radiographic progression. Although a control group was not available, the observed progression rate compared favorably with that seen by the authors in a historical group of 94 patients with polyarticular JIA, 93% of whom had received MTX. These findings, which deserve confirmation in a controlled trial, suggest that etanercept may have a greater disease modifying effect than MTX in JIA.

#### **WHAT IS THE POTENTIAL PLACE OF RADIOGRAPHIC ASSESSMENT IN FUTURE JIA CLINICAL TRIALS?**

Based on clinical experience and existing data, a clinical trial in JIA should be conducted for at least 12 months to demonstrate sufficient radiographic progression to use it as a primary endpoint. Radiographic progression during the first 12 months of followup, as measured with the Poznanski score, was found to predict longterm joint damage and physical functional disability in children with polyarticular-course JIA<sup>15</sup>. Similarly, the change in the adapted Sharp-van der Heijde score during the first year of observation was significantly correlated with the clinical indicators of longterm joint damage and with the amount of radiographic damage at 5 years<sup>20</sup>. In case a longterm extension of the trial is planned, radiographic assessment should be repeated every 12 months. When choosing the radiographic scoring system to be used in the trial, the investigators should take into account the relative advantages and disadvantages of the available methods and their potential ability to detect radiographic change within the timeframe of the trial. In the author's opinion, the adapted Sharp-van der Heijde score<sup>20</sup> is the most comprehensive and reliable of the existing methods and has shown the best properties in terms of reproducibility, construct validity, and capability to detect radiographic progression over time in children with JIA. Use of a single scoring system would greatly facilitate standardization of radiographic assessment in multiple sites and com-

parison between studies, similar to the use of the Pediatric 30 criteria American College of Rheumatology<sup>43</sup>.

## CONCLUSION

In 1992, commenting on the controlled trial by Giannini, *et al*<sup>28</sup> that established the efficacy of MTX in JIA, White and Ansell raised the criticism that the ability of the drug to prevent structural joint damage was not investigated<sup>44</sup>. At that time, however, no reliable radiographic scoring system for JIA was available. In the subsequent 15 years, a large body of data has accumulated, indicating that standardized assessment of radiographic progression in children with chronic arthritis is feasible. As for adult RA, in recent years there has been a growing interest in the use of new imaging techniques, such as magnetic resonance imaging and ultrasound, in children with JIA<sup>45,46</sup>. However, although these techniques are promising, experience with their use in pediatric patients is still very limited. Thus, they are unlikely to replace plain radiography as the standard for evaluating joint damage in JIA for some time to come.

There is now evidence that radiographic damage can be scored reliably in children with JIA. This supports the inclusion of assessment of radiographic progression in future controlled clinical trials in JIA.

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