Quantitative Magnetic Resonance Imaging of the Hands and Wrists of Children with Juvenile Rheumatoid Arthritis

T. BRENT GRAHAM, TAL LAOR, and BERNARD J. DARDZINSKI

ABSTRACT. ***Objective.*** To assess feasibility of measuring synovial volume in the hand and wrist in patients with polyarticular course juvenile rheumatoid arthritis (JRA) by magnetic resonance imaging (MRI). As well, to compare clinical variables with synovial volume calculated from MRI in patients receiving disease modifying or biologic therapy.

Methods. Ten patients with polyarticular course JRA starting methotrexate (n = 3) or etanercept (n = 7) therapy had MRI with intravenous contrast performed of one hand and wrist at baseline and after 6 weeks and 3 months of pharmacotherapy. Synovial volume was determined for the entire hand and wrist and also for regions. Patients were assessed clinically by the core set of outcome variables for JRA and total hand swelling score, and assessed for clinical improvement based upon change in these variables.

Results. Increased synovial volume was observed at entry by MRI in all patients (range 2.4–12.5 cc, median 3.7 cc). Correlation of total synovial volume from MRI with total hand swelling score at each timepoint was good (r = 0.52–0.68). Correlation with other clinical variables was not consistently strong. Patients who improved clinically did not differ from patients who did not improve clinically with respect to change in synovial volume.

Conclusion. Determining synovial volume in the hand and wrist in patients with JRA by MRI is feasible and correlates with total hand swelling assessed on physical examination. Inconsistent or poor correlation with other clinical variables and the clinical definition of improvement requires further study. (J Rheumatol 2005;32:1811–20)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS MAGNETIC RESONANCE IMAGING

Juvenile rheumatoid arthritis (JRA) represents a group of heterologous autoimmune diseases that have in common chronic inflammatory arthritis and have a prevalence of roughly one in 1000 children[1]. The result of persistent synovitis is joint destruction, pain, and loss of function[2]. Advances in therapy in the last 10 years are likely to improve short and longer term outcomes[3,4]. In addition, new methods for assessing whether a patient has improved, such as the American College of Rheumatology (ACR) Pediatric 30 definition of improvement, have increased the trialist's ability to recognize effective agents[5]. However, most outcome variables that meet the definition of improvement in JRA are subjective[5]. Serum indicators of inflammation may fail to reflect disease activity[6,7]. Objective, quantitative measures may be beneficial in assessing disease activity, individual response to therapy, efficacy of treatment in clinical trials, and eventual longer term outcomes.

Magnetic resonance imaging (MRI) has been used to assess disease activity in hands, wrists, and knees of patients with various arthritides[8-15]. MRI is superior to conventional radiography for showing clinically silent and radiographically inapparent lesions[16]. Soft tissue changes, including synovial proliferation, meniscal abnormalities, and articular cartilage thinning and erosion, are clearly shown by MRI[16,17]. Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), an intravenous contrast agent used for MRI, is distributed mainly in the extracellular space and accumulates in areas of increased blood flow as well as increased vascular permeability. Based on this property, Gd-DTPA is used to identify areas of synovial inflammation and to differentiate synovium from joint fluid. Little, if any, synovial enhancement is seen in the joints of children or adults without arthritis[7,15].

In adult rheumatoid arthritis (RA), quantitative assessment of synovitis by use of intravenous Gd-DTPA in the

From the Department of Pediatrics, Division of Rheumatology; Department of Radiology; and the Imaging Research Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Supported by a Trustees grant from the Cincinnati Children's Hospital Medical Center.

T.B. Graham, MD, MS, Department of Pediatrics, Division of Rheumatology; T. Laor, MD, Department of Radiology; B.J. Dardzinski, PhD, Department of Radiology, Imaging Research Center, Cincinnati Children's Hospital Medical Center.

Address reprint requests to Dr. T. Brent Graham, Division of Rheumatology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229-3039.
E-mail: brent.graham@cchmc.org

Accepted for publication April 20, 2005.

wrist and finger joints has proven useful in assessing disease activity and response to therapy. Synovial volume measurements have been used in adults with RA to evaluate disease activity in the wrist and fingers while undergoing drug therapy[18-20]. Synovial volume measured by MRI has been found to be superior to clinical and laboratory assessment in predicting progressive joint destruction in RA[18,21].

In polyarticular course JRA, hand involvement tends to reflect overall disease activity. Initial involvement of the small joints of the hand may bode a poor prognosis[22]. Limiting disability during longterm followup involves the hand more frequently than any other area[23]. The small joints of the hand can be used to measure the efficacy of systemic therapy, especially in patients who have undergone intraarticular injection of corticosteroids into large joints. Joints that have been injected are not considered assessable for measuring outcome of systemic therapy. Unfortunately, clinical assessment of disease activity in the small joints of the hand is particularly prone to disagreement among clinicians[24].

We investigated the feasibility of using MRI as an objective, quantitative method to assess synovial activity in the hands and wrists of children with JRA. To our knowledge, no studies to date have utilized this quantitative technique in children with JRA. Our aim was to obtain measurements of synovial volume using a semiautomated segmentation program from the small joints of the hands and wrists. We hypothesized that synovial volume would correlate with clinical outcome variables. Further, we hypothesized that children with polyarticular JRA who met the clinical definition of improvement 3 months after beginning disease modifying antirheumatic drug (DMARD) or biologic therapy would have a greater reduction in synovial volume of the hand and wrist calculated from MRI than patients who did not improve clinically.

MATERIALS AND METHODS

Patients. Enrollment criteria for the study included a diagnosis of polyarticular course JRA according to ACR criteria[25]. Each child was required to have at least 3 active joints with at least one active joint in the hand or wrist. Only children who could undergo MRI without sedation were enrolled. The Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board approved the study, and informed written consent was obtained from a parent for each child.

All children were recruited from the CCHMC rheumatology clinic. Twelve children initially were entered, and 10 completed the study (9 girls, 1 boy; mean age 11.1 yrs, range 5.2–15.7 yrs). Each child was to begin methotrexate or etanercept therapy based on clinical indications as determined by their attending pediatric rheumatologist. In addition to systemic therapy, one child (Patient 5) also underwent injection of triamcinolone hexacetonide into the fourth proximal interphalangeal joint immediately after the initial MRI examination based upon the clinical examination.

Clinical assessment. Patients underwent rheumatologic examination at entry into the study, and at about 6 weeks and 3 months after initiation of the DMARD or biologic therapy. Clinical assessment was performed on the same day as MR imaging. This assessment was repeated at each visit by the same rheumatologist for each patient. Assessment included total number of active joints, total joints with limitation of motion, physician global assessment of overall disease severity, parent global assessment of overall disease severity, and Childhood Health Assessment Questionnaire (CHAQ) disability index[26]. Physician and parent global assessments were scored on a scale of 0 to 10, a score of 10 equaling "severe symptoms." A parent completed the CHAQ disability index. An active joint was defined as the presence of swelling or, in the absence of swelling, limitation of motion accompanied by tenderness or pain on motion. Each joint in the imaged hand was also graded on a 0–3 severity scale for swelling (0 = none, 1 = minimal, 2 = swelling remaining within the joint margin, 3 = bulging). The sum of these scores was utilized to determine a total hand swelling score (range 0–48). The examining rheumatologists were blinded to results of imaging assessment, and radiologists were blinded to the results of clinical assessment. Laboratory assessment included Westergren erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

The clinical and laboratory variables were combined to determine whether the child should be classified as improved or not improved after initiation of medical therapy. To meet the definition of improvement, a patient had to have improvement of at least 30% in at least 3 of the 6 core set variables, and not more than one variable could worsen by more than 30%. For ESR to be utilized as a criterion for improvement, the value at baseline had to be outside the normal range (0–10 mm/h). These criteria are identical to the ACR Pediatric 30, with the exception that parent global assessment of disease severity was substituted for parent global assessment of overall well being[5].

MR imaging. Each child underwent serial MRI of the more symptomatic hand and wrist just prior to initiation of treatment with methotrexate or etanercept, and after roughly 6 weeks and 3 months on therapy. One child was imaged only at initiation and 3 months of therapy, and one child's images at the 6 week point were of poor quality due to hardware difficulties. For this reason, only initial and final MRI examinations for each child (total of 20 examinations) were utilized for the primary data analysis.

MRI was performed on a 1.5 T clinical scanner (General Electric Medical Systems, Milwaukee, WI, USA). Twenty-nine scans were successfully completed over a 22 month period using a quadrature extremity transmit-receive coil (IGC Medical Advances, Milwaukee, WI, USA). Prior to the beginning of the scan, an intravenous catheter was placed in the upper extremity opposite the side to be imaged. At the time of catheter placement, blood was drawn for the laboratory studies. Each child was placed in a prone position with the hand of interest outstretched overhead. The imaging protocol is outlined in Table 1. Total scan time was about 25 min. Prior to the 3-dimensional GRE sequence, contrast was administered intravenously by hand injection bolus (0.1 mmol/kg body weight; Gd-DTPA, Magnevist, Berlex Inc., Wayne, NJ, USA). All sequences performed following intravenous contrast were completed within 10 min of the bolus administration.

Fields of view ranged from 16 to 20 cm in the frequency direction and 12 to 15 cm in the phase-encoding direction. The Fast Dixon sequence was protocoled with a 256×192 matrix and 5 mm slice thickness with a 1.5 mm gap. The voxel volume varied from 1.90 to 3.17 mm^3 depending on the field of view used. The conventional spin echo T1-weighted sequence following intravenous contrast was protocoled with a 256×160 matrix, 4 mm slice thickness, and 1.0 mm gap. The voxel volume varied from 2.34 to 3.66 mm^3 depending on the field of view used. Typically, for a 2 cc volume, roughly 719 brightest voxels would have to be segmented.

MRI data analysis. *Synovial volume quantification*. MRI were reviewed for excessive patient motion and were used to guide the quantitative assessment. Imaging sequences were optimized for quantitative synovial measurements, not for qualitative analysis of cartilage or bone erosions.

The wrist and hand were divided into 4 zones: radiocarpal-proximal metacarpal (RCM), distal metacarpal-phalangeal (MP), proximal and distal interphalangeal (IP), and tendon (Figure 1A). Synovial volumes were calculated for each imaging examination from the fat suppressed, contrast enhanced imaging sequences using the semiautomated volume segmenta-

Table 1. MR imaging protocol.

Sequence	TR, ms	TE, ms	Matrix	Bandwidth, kHz	Echo Train Length	Signal Averages (NEX)	Slice Thickness/ Spacing, mm
Coronal FSE PD	2000	Minimum	256 × 192	16	8	2	3/1
Coronal SE T1	400	Minimum full	256 × 160	16	NA	1	4/1
3-D GRE*	5.4	1.5	128 × 128 × 12	32	NA	0.5	5/0
Coronal SE T1*	400	Minimum full	256 × 160	16	NA	1	4/1
Coronal Fast Dixon T1*	500	17	256 × 192	16	3	1	5/1

* Following intravenous contrast administration. FSE: fast spin-echo, PD: proton density, CSE: conventional spin-echo, GRE: gradient recalled echo, NA: not applicable.

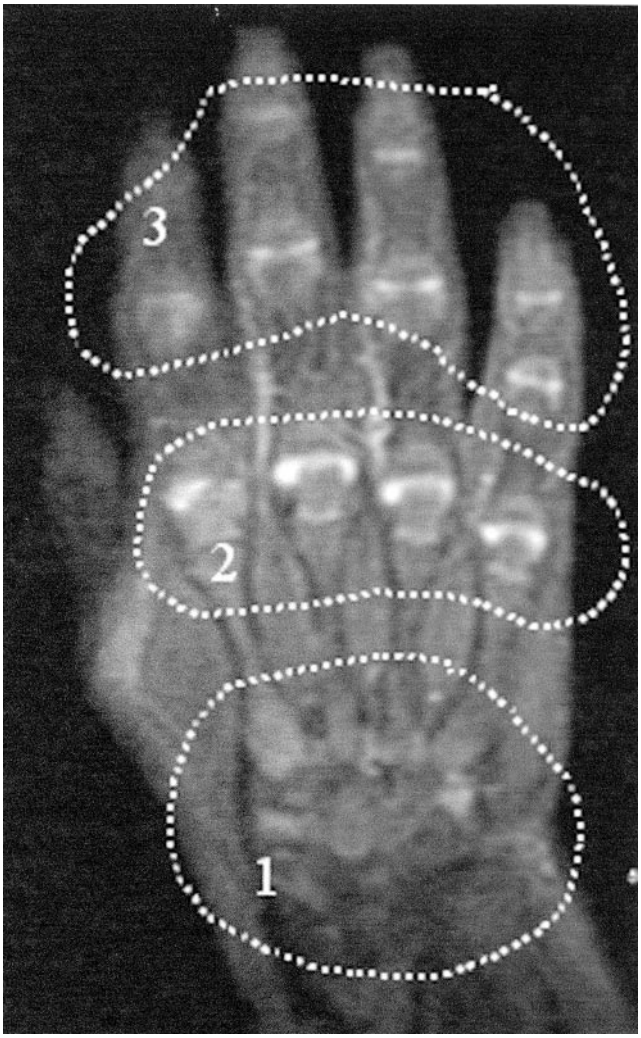

Figure 1. Three regions of interest outlined on a fat suppressed coronal T1-weighted image of the hand following intravenous contrast administration: 400/14 (repetition time, TR, ms/echo time, TE, ms), 4/1 (slice thickness mm/gap thickness mm), 256 × 160 matrix, 20 cm field of view (FOV). Region 1 includes the distal radiocarpal and carpal-proximal metacarpal joints; region 2 includes the distal metacarpal-phalangeal joints; region 3 includes the proximal and distal interphalangeal joints.

tion program, Cincinnati Children's Hospital Imaging Processing Software [CCHIPS computer program, written in Interactive Data Language (IDL; Research Systems Inc., Boulder, CO, USA) is available free on the CCHMC Imaging Research Center website at www.irc.cchmc.org/cchips_main.htm. This program works for DICOM files.]. In most cases, the synovial volume was calculated from the Fast Dixon sequence. In the event of motion artifact, the conventional spin echo T1-weighted sequence was used.

Regions of interest (ROI) for each zone were drawn by a single operator around the high signal intensity synovium (Figure 2A). Care was taken to exclude high signal intensity from adjacent blood vessels, bone marrow edema, soft tissues, and cartilage. Boundaries were shrunk down around the bright signal areas within the user-defined ROI using a k-means-clustering algorithm[15,27] (Figure 2B). Synovial volume was calculated from the number of brightest pixels that were automatically segmented by multiplying the in-plane pixel dimensions by the slice thickness. Synovial volumes for each of the 4 zones and total synovial volume were calculated for each child at each MRI examination. Change in synovial volume (cc) and as a percentage of initial volume over time was determined. Variation of synovial volume calculation was determined by having 2 observers define ROI for MCP region for one patient and tendon region for another patient 10 times. Coefficient of variation was then determined for the synovial volume calculations for each region for one observer and for 2 observers.

Correlation of clinical assessment and MRI data. Synovial volume obtained from the MRI examinations at Time 0 and 3 months and percentage change over time were correlated with clinical variables (SPSS v. 11.5 for Windows; SPSS Inc., Chicago, IL, USA). Pearson correlation was utilized for all variables except parent and physician global assessments at Time 0 and Time 3 months, for which the Spearman rank correlation was used to evaluate nonparametric data. Student t test was used to compare change in synovial volume in patients who met the clinical definition of improvement with change in synovial volume in patients who did not improve. Alpha level of 0.05 was set for significance. For analysis of variation both within and between observers, coefficient of variation was calculated.

RESULTS

Clinical assessment. The results of the clinical assessment and laboratory tests for each patient are shown in Table 2. Seven of 9 children who had CRP measured at their initial visit had normal values, necessitating use of the ESR as the serum measure of inflammation for defining improvement. One patient (Patient 8) did not have laboratory variables measured. ESR would not have affected this patient's meeting the clinical definition of improvement. Seven patients (6 girls, one boy) met the clinical definition of improvement, and 3 did not. Baseline assessments in the children who

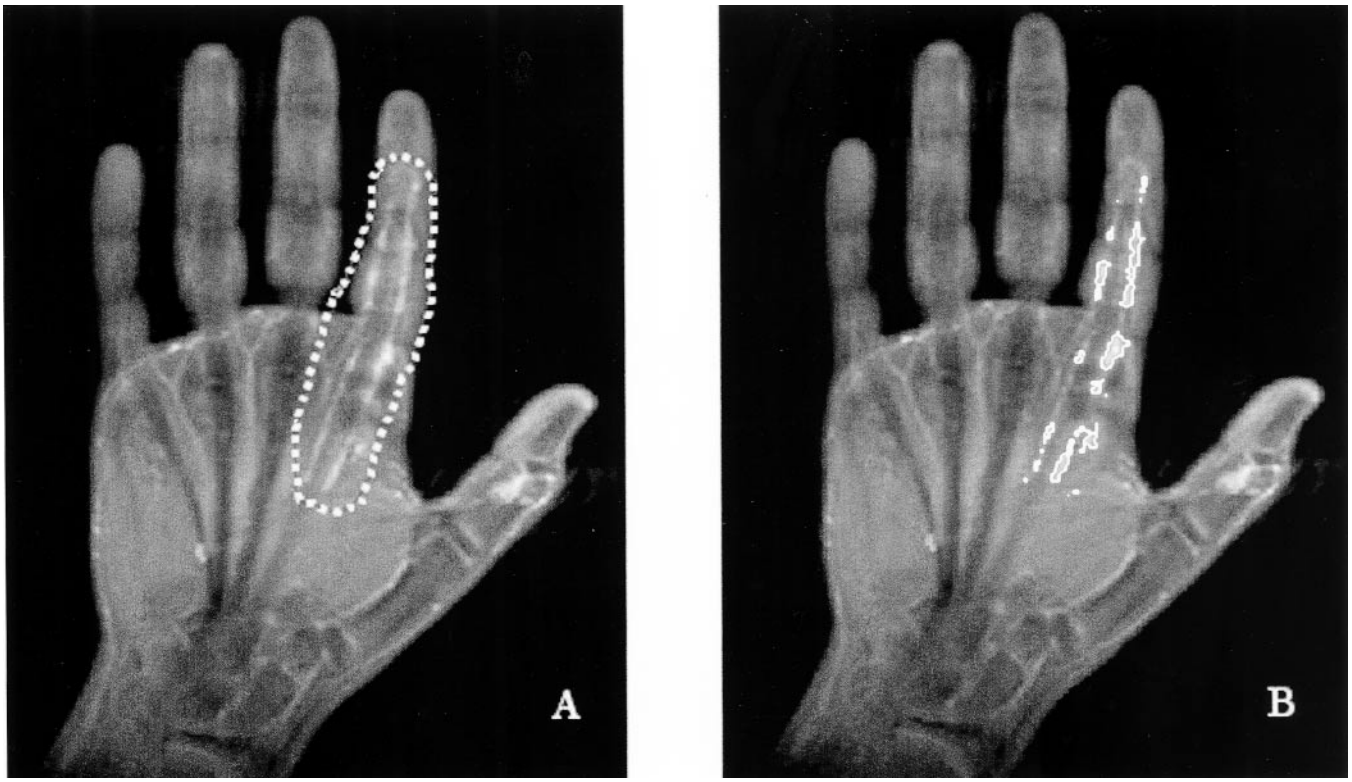

Figure 2. Coronal fat suppressed T1-weighted image of the hand following intravenous contrast administration shows synovial enhancement around the flexor tendon of the second digit and at the interphalangeal joint of the thumb (400/14 TR/TE, 4/1 slice thickness mm/gap thickness mm, 256 × 160 matrix, 18 cm FOV). (A) Operator-drawn region of interest around the enhancing synovium of the second flexor tendon. (B) Automated computer segmentation of the brightest pixels in the region of interest drawn around the second flexor tendon in A.

improved clinically were similar to children who did not demonstrate clinical improvement.

MRI data analysis. Total synovium volume. All patients had measurable synovial volume at study entry. Total synovial volume ranged from 2.3 to 12.4 cc (median 3.7 cc) at initial MRI examination, and 1.1 to 13.2 cc (median 2.2 cc) at final MRI examination. The greatest synovial volume was measured in the RCM and tendon regions (maximum values 4.8 cc and 4.9 cc, respectively). Three children showed no change of absolute value > 0.3 cc in overall synovial volume. Total synovial volume decreased in 6 children from initial to final MRI examination, with a volume change range of 0.6–3.0 cc (25%–73%; Figure 3). One child had an overall increase in synovial volume over time of 0.7 cc (6%). Total synovial volume at the 6 week timepoint in 8 children measured 1.34–13.49 ml. Change in synovial volume from Time 0 to Time 6 weeks correlated well with the change in synovial volume from Time 0 to 3 months ($r = 0.699$, $p = 0.054$).

Radial-carpal-metacarpal region. With the exception of one child, all showed abnormal synovial enhancement of the RCM region at the start of the study. Synovial volume in those with abnormal synovial enhancement ranged from 0.8 to 4.8 cc (median 1.9 cc). Five children showed a decrease in synovial volume (13%–77%), 2 showed an increase in synovial volume (28%–69%), and 3 children showed no change of absolute value > 0.3 cc in synovial volume over time (Figure 4).

Metacarpal-phalangeal region. At initiation into the study, 4 children had ≤ 0.3 cc of measurable synovium at the MCP region. Synovial volume of the MCP region ranged from 0.2 to 1.7 cc (median 0.6 cc). Two children showed a decrease in synovial volume (56%–85%), one child showed an increase in synovial volume (24%), and 7 children had no change > 0.3 cc in synovial volume over time (Figure 5).

Interphalangeal region. At initiation into the study, 4 children had ≤ 0.3 cc of measurable synovium at the IP region. Synovial volume ranged from 0.2 to 2.5 cc (median 0.7 cc). Four children showed a decrease in synovial volume (32%–71%), and 6 children showed no change of absolute value > 0.3 cc in synovial volume over time.

Tendons. At initiation into the study, 4 children had ≤ 0.3 cc of measurable synovium around the tendons of the hand and wrist. Synovial volume ranged from 0 to 4.8 cc (median 0.5 cc). Four children showed a decrease in synovial volume (45%–100%), no child had an increase in synovial volume, and 6 children showed no change in synovial volume > 0.3 cc over time (Figures 6 and 7).

Table 2. Clinical and imaging data.

Patient	Age, yrs	Therapy	Time, mo	Clinical Improvement	Physician Global Assessment	Parent Global Assessment	Total Active Joints	Total Joints LOM	CHAQ[27]	ESR	Total Hand Swelling Score	MRI Synovial Volume, cc
1	10.9	ETAN	0		6	4	19	19	1.4	15	4	2.43
			3		3	2	11	9	1.4	6	2	2.36
Δ, %				Yes	↓50	↓50	↓42	↓53	0	↓60	↓50	↓3
2	12.1	MTX	0		7	5	33	7	1.9	30	20	12.44
			3		5	1	28	23	1.1	11	11	13.15
Δ, %				Yes	↓29	↓80	↓15	↑229	↓42	↓63	↓45	↑6
3	8.8	ETAN	0		2	3	4	4	1.6	10	6	2.3
			5		1	0	3	0	1.2	6	3	1.75
Δ, %				Yes	↓50	↓100	↓25	↓100	↓25	↓40	↓50	↓24
4	12.9	MTX	0		5	3	3	2	1.6	12	3	3.16
			3		3	4	2	2	1.8	6	4	2.09
Δ, %				No	↓40	↑33	↓33	0	↑12	↓50	↑33	↓34
5	6.5	MTX	0		6	NA	6	7	3.2	126	4	4.40
			3		3	4	7	4	2.8	84	3	4.14
Δ, %				Yes	↓50	NA	↑17	↓43	↓13	↓33	↓25	↓6
6	12.6	ETAN	0		6	7	15	8	2.4	14	12	4.03
			3		2	4	24	2	2.0	8	11	1.07
Δ, %				Yes	↓67	↓57	↑60	↓75	↓17	↓43	↓8	↓73
7	14.3	ETAN	0		3	2	7	15	1.6	7	3	3.39
			3		2	3	5	11	1.2	6	2	1.63
Δ, %				No	↓33	↑50	↓29	↓27	↓25	↓14	↓33	↓52
8	5.2	ETAN	0		4	5	36	5	1.9	NA	10	3.41
			3		1	3	18	1	1.2	NA	4	3.17
Δ, %				Yes	↓75	↓40	↓50	↓80	↓37	NA	↓60	↓7
9	11.8	ETAN	0		2	3	6	3	1.5	18	2	4.29
			3		3	5	11	7	1.5	4	1	1.77
Δ, %				No	↑50	↑67	↑83	↑133	0	↓78	↓50	↓59
10	15.7	ETAN	0		4	7	6	2	2.6	6	4	6.82
			3		1	1	3	1	1.0	3	2	4.56
Δ, %				Yes	↓75	↓86	↓50	↓50	↓62	↓50	↓50	↓33

CHAQ: Childhood Health Assessment Questionnaire, MTX: methotrexate, ETAN: etanercept, LOM: limitation of motion, ESR: erythrocyte sedimentation rate, NA: not applicable.

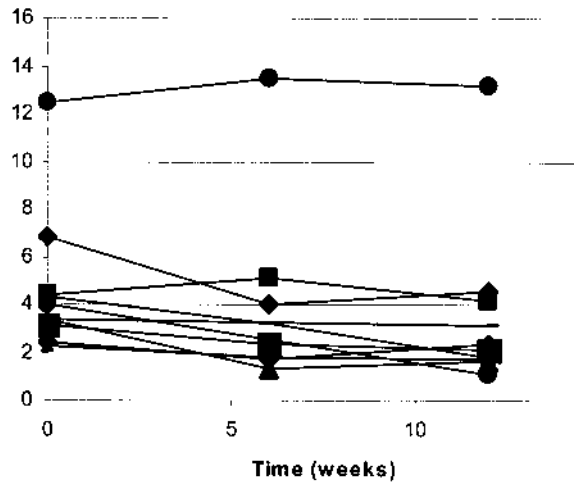

Figure 3. Over the course of the study, one patient showed increase in synovial volume; 3 patients had no change in synovial volume > 0.3 cc; 6 patients had decreases in synovial volume ranging from 25% to 73%.

Variation. Coefficients of variation for the MCP region were 7.6% and 13.9% for the individual readers and 11.2% for 2 readers. Coefficients of variation for the tendons region were 13.4% and 10.8% for the individual readers and 11.9% for 2 readers.

Correlation of clinical assessment and MRI data. Total synovial volumes as a function of total hand swelling score and as a function of total active joints were plotted for 0 and 3 months after initiation of therapy (Figures 8 and 9).

At Time 0, synovial volume calculated from MRI correlated significantly with total hand swelling score ($r = 0.72$, $p < 0.05$). Trends toward correlation with parent global assessment and total active joints were modest ($r = 0.55$ and $r = 0.44$, respectively). At Time 3 months, synovial volume correlated well with total joints with limited range of motion ($r = 0.76$, $p < 0.05$). Trends toward correlation with total hand swelling score and total active joints were modest ($r = 0.52$ and $r = 0.53$, respectively). Correlations with other clinical and laboratory assessment variables at each timepoint were

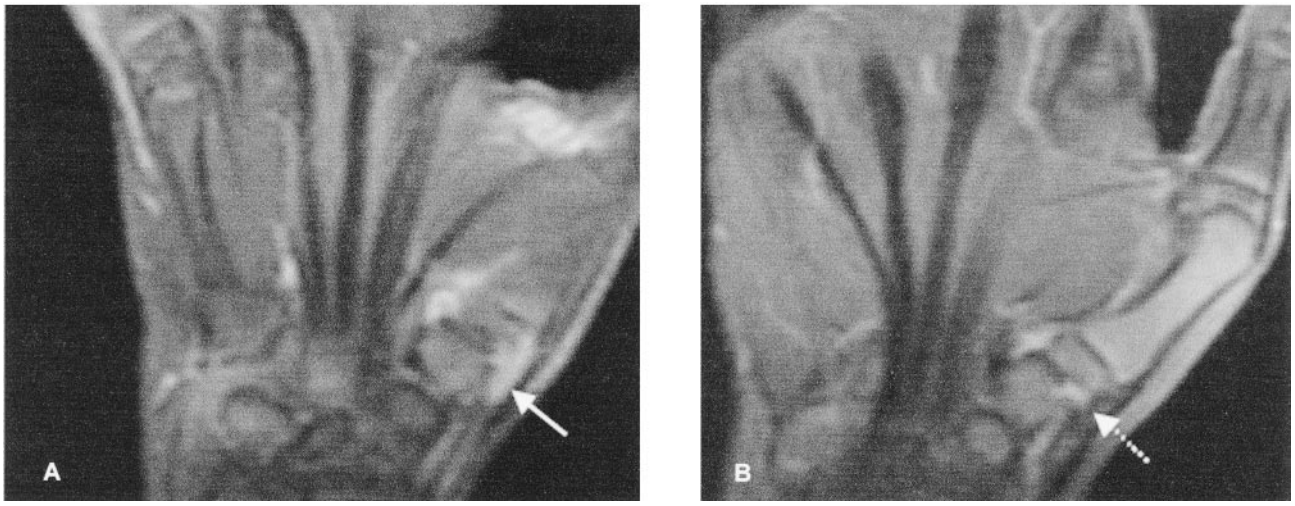

Figure 4. Coronal fat suppressed T1-weighted images (400/14 TR/TE, 4/1 slice thickness mm/gap thickness mm, 256 × 160 matrix, 16 cm FOV) with intravenous contrast from an 11-year-old girl (Patient 9) (A) at study onset and (B) 3 months later. Note the decrease in the volume of enhanced synovium at the carpal-metacarpal joint of the thumb (solid arrow on initial examination, broken arrow at followup).

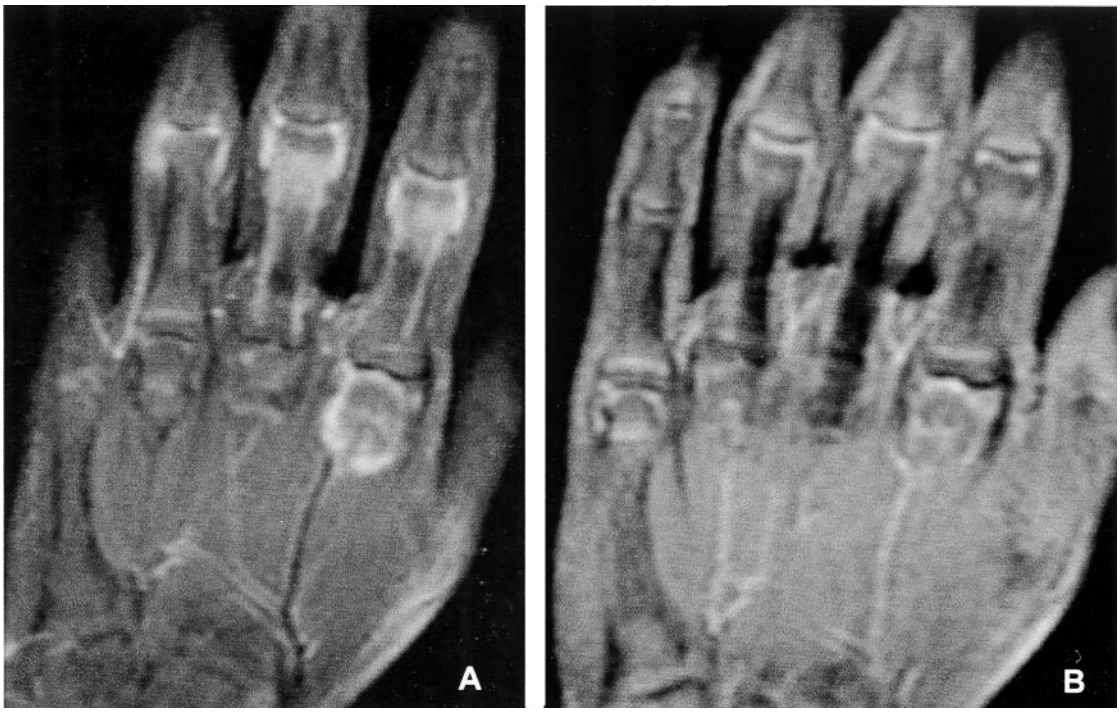

Figure 5. Coronal fat suppressed T1-weighted images (400/14 TR/TE, 4/1 slice thickness mm/gap thickness mm, 256 × 160 matrix, 18 cm FOV) following intravenous contrast administration of the hand of a 12-year-old girl (Patient 6) at study onset (A) and 3 months later (B). There has been a decrease in the amount of enhancing synovium of the first metacarpal-phalangeal and interphalangeal joints over time.

not strong (range: r = –0.22 to 0.38). At Time 6 weeks, correlations with total active joint count, total hand swelling score, and physician global assessment were strong (r = 0.95, $p < 0.001$; r = 0.94, p = 0.001; and r = 0.85, $p < 0.01$, respectively).

Percentage change in each of the components of the clinical definition of improvement was compared with percentage change in synovial volume calculated from MRI from Time 0 to Time 3 months. None of these correlations was significant, and most showed negative correlation (range: r = –0.58 to 0.18). Similar findings were present analyzing the change from Time 0 to Time 6 weeks, but modest positive correlations were observed between change in synovial volume and change in total active joints (r = 0.58) as well as change in joints with limited range of motion (r = 0.55).

Children who met the clinical definition of improvement

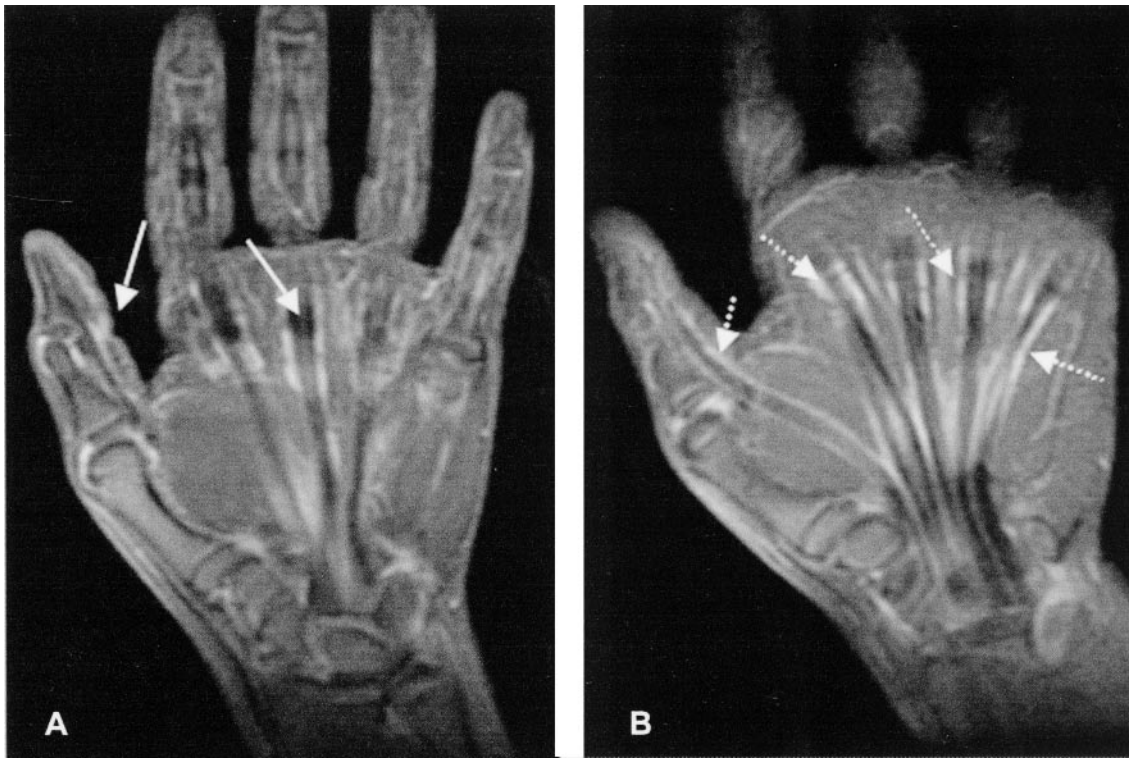

Figure 6. Coronal fat suppressed T1-weighted image (400/14 TR/TE, 4/1 slice thickness mm/gap thickness mm, 256 × 160 matrix, 18 cm FOV) of the hand and wrist with intravenous contrast of a 12-year-old boy (Patient 2) with increased synovial enhancement of all regions. Note the tenosynovitis (arrows) at initiation of the study (A). After 3 months (B), there was no significant change in the volume of synovium surrounding the flexor tendons (broken arrows).

did not differ from patients who did not with respect to percentage change in synovial volume over time. Indeed, the 3 children who did not meet the clinical definition of improvement showed a trend toward greater decrease in synovial volume compared to patients who did meet the clinical definition of improvement (mean 48% ± 13% vs 20% ± 27%; p = 0.13). Post-hoc power calculation indicated that this sample size would have a 40% power to detect this difference (28%) in change in synovial volume between the 2 groups if such a difference existed.

DISCUSSION

All but one MRI examination was considered diagnostic and yielded imaging data for which synovial volume analysis was successful for children with JRA. With the exception of 2 children (ages 5 and 8 years) who were unable to remain still for the duration of the imaging examination and chose not to continue in the study after the first visit, all children were imaged successfully.

Synovial volume calculated from MRI correlated reasonably well with total hand swelling score and total number of active joints at each timepoint. Correlation with the other variables in the core set of outcome variables was not consistently strong. The correlation with total active joints is encouraging, as this correlation argues for the utility of the hand and wrist as a surrogate marker for total burden of synovitis in patients with polyarticular disease. Lack of strong correlation with laboratory values and physician and parent global assessments may reflect the insensitivity of the former, and subjectivity of the latter.

Change in the clinical variables did not correlate well with change in synovial volume calculated from MRI. Several possibilities for this discrepancy exist. We did not evaluate a placebo group. Bias toward clinical improvement likely had some effect on the assessment by parents and physicians. The clinical assessment is based on relatively subjective measures, with the exception of laboratory values. In addition, the low hand swelling score on clinical examination at entry in some patients may make evaluation of systemic response by change in total hand synovial volume less valid in these patients.

Inaccuracy of measurement from the MRI data may also contribute to the lack of correlation with clinical assessment over time. Although the MRI analysis is based on objective computer analyses, subjective user input determines the areas to be quantified. The automated segmentation program is based on absolute pixel signal intensity; however, initially, ROI are selected by an operator. It is likely that increased signal intensity from some smaller blood vessels was incorporated into the measurements. The same vessels were present across all imaging examinations for a given patient, and, as they would not change volume over time, their contribu-

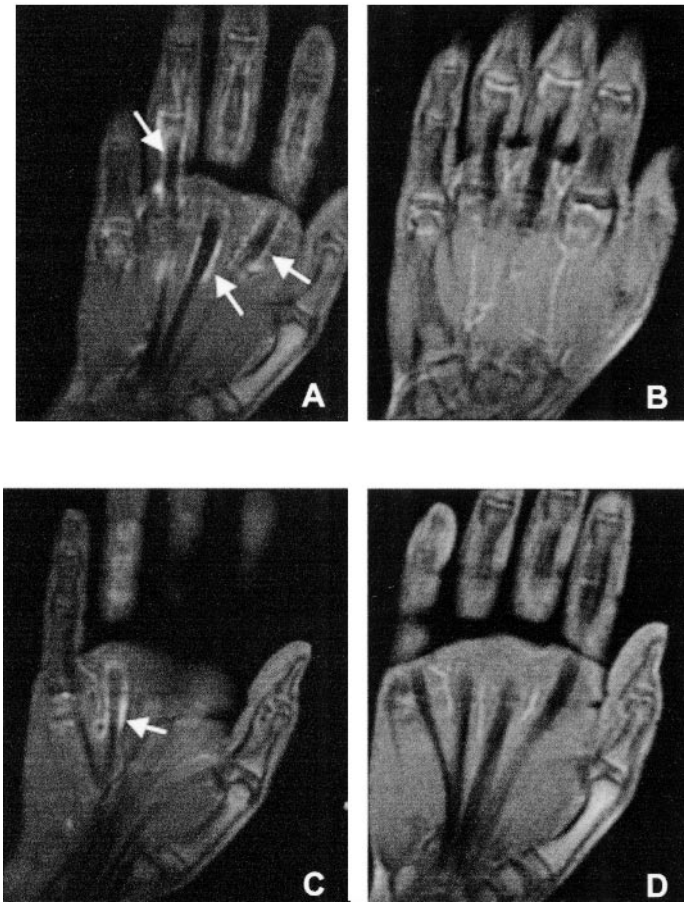

Figure 7. Coronal fat suppressed T1-weighted images (400/14 TR/TE, 4/1 slice thickness mm/gap thickness mm, 256 × 160 matrix, 18 cm FOV) following intravenous contrast from a 12-year-old girl (Patient 6). Initial images (A, C) show tenosynovitis of the 2nd, 3rd, and 4th digits (arrows). Followup examination (B, D) showed marked improvement in the tenosynovitis.

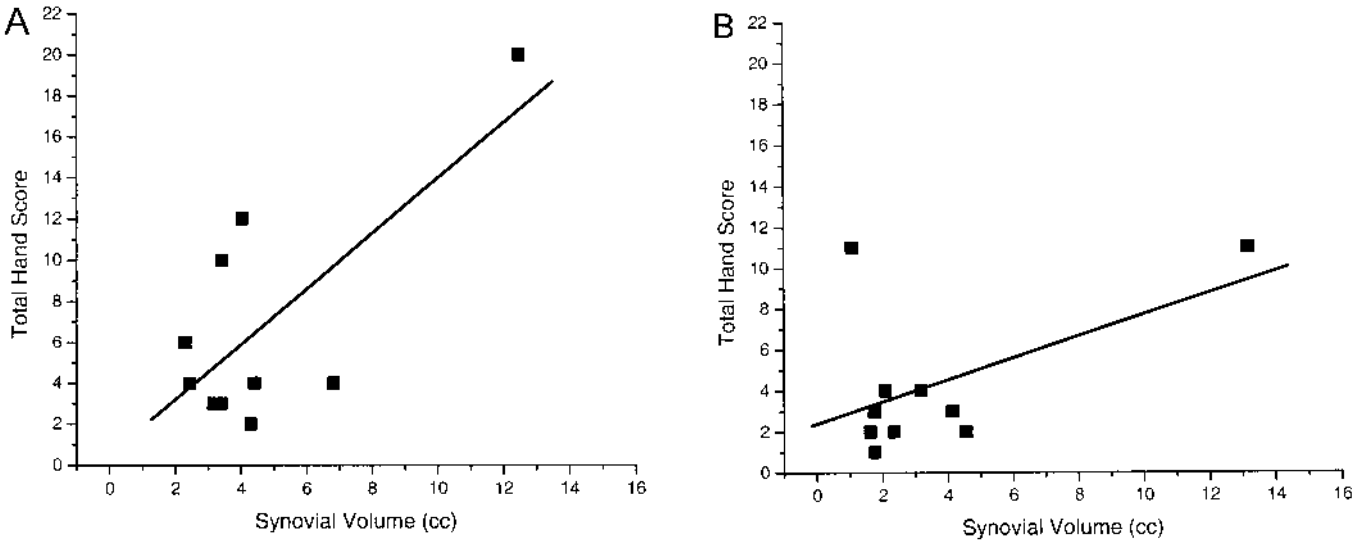

Figure 8. A. Total hand swelling score versus synovial volume at Time 0 (r = 0.72). B. Total hand swelling score versus synovial volume at Time 3 months (r = 0.52).

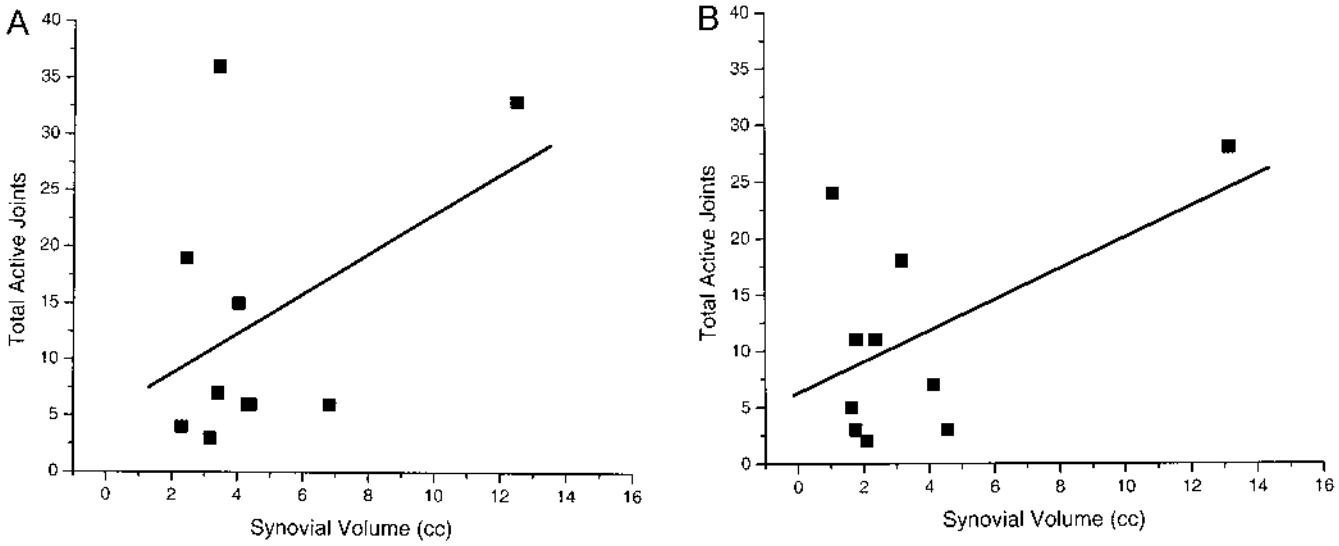

Figure 9. A. Total number of active joints versus synovial volume at Time 0 (r = 0.44). B. Total number of active joints versus synovial volume at Time 3 months (r = 0.53).

tion to a change in measured volume is thought to be negligible. The same operator defined the ROI for each patient at each examination, so interobserver bias would be minimized. The technique for determining synovial volume is based on the brightest pixel signal intensity. However, as synovial disease activity diminishes, it becomes less vascular and thus less hyperintense on MRI[8,11]. This may contribute to an underestimation of synovial volume by the segmentation technique. The small volume of synovium in the hand and wrist of children also likely contributes to the difficulty of precise demarcation of ROI.

Because of the frequent small access sites in children, we decided to hand-inject the intravenous contrast. Although the technique was repeated from child to child, precise reproducible injection rates of contrast were not controlled. This is likely of little significance when measuring volume, as studies have shown that measuring volume based on signal intensity of enhancing synovium is considered acceptable when images are acquired within 10 minutes of contrast injection[28]. For the MR imaging, the children were positioned prone with the hand of interest located as centrally in the core of the magnet as possible. This made identical positioning more difficult, particularly with the younger children. Inclusion of the entire volume of the hand obviated the need for identical slice location between MRI examination times and minimized the effects from partial volume averaging. The use of 5 mm slices with 1 mm gaps was needed to limit overall sequence times. Limiting overall sequence time was important for the younger children who were imaged without sedation. This slice thickness did add a component of volume averaging; however, since identical scanning parameters were used with each examination, any potential volume averaging would be consistent across scans for any given child.

Lack of correlation with clinical variables is not entirely surprising. MRI assessment of synovitis in the wrist and hand in RA has only modest correlation with clinical examination of these joints, and weak correlation with other clinical and laboratory measures[7,18,29]. Nevertheless, synovial volume has been shown to be superior to clinical and laboratory assessment in predicting the development of erosions in these patients[18,21]. Also, synovial volume in the knee in adults with RA and osteoarthritis correlates with histologic findings of synovial inflammation at arthroscopy[30]. In addition, synovial volume is only one aspect of MRI assessment of disease activity, and rate of enhancement as well as bone edema are likely important as well[8,11,31].

It is also possible that a lag exists between the improvement in active synovial disease identified on MRI and improvement that is reflected in clinical variables. Huh, *et al* compared patients in clinical remission with those not in clinical remission after a mean of 17 months of treatment, and found a difference in synovial volume in the wrist between the groups[20]. Quantifying synovial volume later in the course of therapy may be more accurate in assessing change over time.

Our synovial volume data show that synovitis in the wrist and tendons contributes substantially to total hand synovial volume on MRI; however, synovitis in these areas contributes less to counts of active joints and joints with limited range of motion currently utilized for the ACR Pediatric 30[5]. In particular, synovial inflammation surrounding tendons of the hand is not taken into account, and can contribute substantially to the overall volume of disease activity. MRI may provide additional information with respect to the extent of disease activity, particularly for joints affected by tenosynovitis.

A major limitation of our study was the small sample size. As this was an exploratory trial, the power to detect a

difference between responders and nonresponders with respect to change in synovial volume was limited.

In summary, we found that using MR imaging as a quantitative measure of disease activity in the hands and wrists of children with JRA is feasible and correlates with total hand swelling assessed on physical examination. Inconsistent or poor correlation with other clinical variables and the clinical definition of improvement requires further study. Synovial volume measurement may be a useful addition to, but not a replacement for, the ACR Pediatric 30.

ACKNOWLEDGMENT

We acknowledge Drs. David Glass, Tom Griffin, Daniel Lovell, and Murray Passo for performing clinical examinations for this study, Dr. Edward Giannini for guidance in statistical analysis, and Kendall O'Brien, RT, for performing the MR imaging.

REFERENCES

1. Gare B. Juvenile arthritis: who gets it, where and when? A review of current data on incidence and prevalence. Clin Exp Rheumatol 1999;17:367-74.
2. Gare B, Fasth A. The natural history of juvenile chronic arthritis: a population based cohort study. II: outcome. J Rheumatol 1995;22:308-19.
3. Giannini E, Brewer E, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis: Results of the USA-USSR double-blind, placebo-controlled trial. N Engl J Med 1992;326:1043-9.
4. Lovell OJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N. Engl J Med 2000;342:763-9.
5. Giannini E, Ruperto N, Ravelli A, Lovell D, Felson D, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40:1202-9.
6. Giannini E, Brewer E Jr. Poor correlation between the erythrocyte sedimentation rate and clinical activity in juvenile rheumatoid arthritis. Clin Rheumatol 1987;6:197-210.
7. Savnik A, Malmskov H, Thomsen H, et al. Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases. J Rheumatol 2001;28:2193-200.
8. Konig H, Sieper J, Wolf K-J. Rheumatoid arthritis: evaluation of hypervascular and fibrous pannus with dynamic MR imaging enhanced with GD-DTPA. Radiology 1990;176:473-7.
9. Eich G, Halle F, Hodler J, Seger R, Willi U. Juvenile chronic arthritis: imaging of the knees and hips before and after intraarticular steroid injection. Pediatr Radiol 1994;24:558-63.
10. Ostergaard M, Gideon P, Henriksen O, Lorenzen I. Synovial volume — a marker of disease severity in rheumatoid arthritis? Quantification by MRI. Scand J Rheumatol 1994;23:197-202.
11. Gaffney K, Cookson J, Blake D, Coumbe A, Blades S. Quantification of rheumatoid synovitis by magnetic resonance imaging. Arthritis Rheum 1995;38:1610-7.
12. Blebea J, Gylys-Morin V. MR imaging of the knee in juvenile chronic arthritis with fast, 3D and contrast-enhanced imaging techniques [abstract]. Radiology 1996;201:211.
13. Jevtic V, Watt I, Rozman B, et al. Prognostic value of contrast enhanced Gd-DTPA MRI for development of bone erosive changes in rheumatoid arthritis. Br J Rheumatol 1996;35 Suppl 3:26-30.
14. Ostergaard M, Stoltenberg M, Henriksen O. Quantitative assessment of synovial inflammation by dynamic gadolinium-enhanced magnetic resonance imaging. A study of the effect of intra-articular methylprednisolone on the rate of early synovial enhancement. Br J Rheumatol 1996;35:50-9.
15. Gylys-Morin V, Graham T, Blebea J, et al. Knee in early juvenile rheumatoid arthritis: MR imaging findings. Radiology 2001;220:696-706.
16. Herve-Somma C, Sebag G, Prieur A, Bonnerot V, Lallemand D. Juvenile rheumatoid arthritis of the knee: MR evaluation with Gd-DOTA. Radiology 1992;182:93-8.
17. Ostergaard M, Hansen M, Stoltenberg M, et al. New radiographic bone erosions in the wrists of patients with rheumatoid arthritis are detectable with magnetic resonance imaging a median of two years earlier. Arthritis Rheum 2003;48:2128-31.
18. Ostergaard M, Hansen M, Stoltenberg M, et al. Magnetic resonance imaging-determined synovial membrane volume as a marker of disease activity and a predictor of progressive joint destruction in the wrists of patients with rheumatoid arthritis. Arthritis Rheum 1999;42:918-29.
19. Sugimoto H, Takeda A, Kano S. Assessment of disease activity in rheumatoid arthritis using magnetic resonance imaging: quantification of pannus volume in the hands. Br J Rheumatol 1998;37:854-61.
20. Huh YM, Suh JS, Jeong EK, et al. Role of the inflamed synovial volume of the wrist in defining remission of rheumatoid arthritis with gadolinium-enhanced 3D-SPGR MR imaging. J Magn Reson Imaging 1999;10:202-8.
21. Conaghan P, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum 2003;48:64-71.
22. Ruperto N, Ravelli A, Levinson J, et al. Longterm health outcomes and quality of life in American and Italian inception cohorts of patients with juvenile rheumatoid arthritis. II. Early predictors of outcome. J Rheumatol 1997;24:952-8.
23. Ansell B, Wood P. Prognosis in juvenile chronic polyarthritis. Clin Rheum Dis 1976;2:397-412.
24. Guzman J, Burgos-Vargas R, Duarte-Salazar C, Gomez-Mora P. Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. J Rheumatol 1995;22:2331-6.
25. Brewer E Jr, Bass J, Baum J, et al. Current proposed revision of JRA criteria. Arthritis Rheum 1977;20 Suppl:195-9.
26. Singh G, Athreya B, Fries J, Goldsmith D. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;12:1761-9.
27. Bezdek J, Hall L, Clarke L. Review of MR image segmentation techniques using pattern recognition. Med Phys 1993;20:1033-48.
28. Ostergaard M, Klarlund M. Importance of timing of post-contrast MRI in rheumatoid arthritis: what happens during the first 60 minutes after IV gadolinium-DTPA. Ann Rheum Dis 2001;60:1050-4.
29. Bakchaus M, Kamradt T, Sandrock D, et al. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum 1999;42:1232-45.
30. Ostergaard M, Stoltenberg M, Løvgreen-Nielsen P, Volck B, Jensen C, Lorenzen I. Magnetic resonance imaging-determined synovial membrane and joint effusion volumes in rheumatoid arthritis and osteoarthritis: comparison with the macroscopic and microscopic appearance of the synovium. Arthritis Rheum 1997;40:1856-67.
31. McQueen F, Benton N, Perry D, et al. Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. Arthritis Rheum 2003;48:1814-27.