Evaluation of Magnetic Resonance Imaging Responsiveness in Active Psoriatic Arthritis at Multiple Timepoints during the First 12 Weeks of Antitumor Necrosis Factor Therapy

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ABSTRACT. ***Objective.*** To assess the responsiveness of high- and low-field extremity magnetic resonance imaging (MRI) variables at multiple timepoints in the first 12 weeks post-antitumor necrosis factor (anti-TNF) therapy initiation in patients with psoriatic arthritis (PsA) and active dactylitis.

Methods. Twelve patients with active PsA and clinical evidence of dactylitis involving at least 1 digit were recruited. Patients underwent sequential high-field conventional (1.5 Tesla) and extremity low-field MRI (0.2 Tesla) of the affected hand or foot, pre- and postgadolinium at baseline (pre-TNF), 2 weeks (post-TNF), 6 weeks, and 12 weeks. A blinded observer scored all images on 2 occasions using the PsA MRI scoring system.

Results. Eleven patients completed the study, but only 6 patients completed all high-field and low-field MRI assessments. MRI scores demonstrated rapid response to TNF inhibition with score reduction in tenosynovitis, synovitis, and osteitis at 2 weeks. Intraobserver reliability was good to excellent for all variables. High-field MRI demonstrated greater sensitivity to tenosynovitis, synovitis, and osteitis and greater responsiveness to change posttreatment. Treatment responses were maintained to 12 weeks.

Conclusion. This study demonstrates the use of MRI in detecting early response to biologic therapy. MRI variables of tenosynovitis, synovitis, and osteitis demonstrated responsiveness posttherapy with high-field scores more responsive to change than low-field scores. (First Release October 15 2015; J Rheumatol 2016;43:75–80; doi:10.3899/jrheum.150347)

Key Indexing Terms:
PSORIATIC ARTHRITIS MAGNETIC RESONANCE IMAGING PsAMRIS DACTYLITIS

Psoriatic arthritis (PsA) is a condition with diverse manifestations encompassing peripheral inflammatory joint disease, enthesitis, tenosynovitis, and axial disease[1]. Magnetic resonance imaging (MRI) allows unrivaled assessment of disease activity in diverse structures permitting detailed assessment of the protean manifestations of PsA. In addition, and importantly, MRI permits the assessment of response to therapy for each manifestation[2].

Accordingly, scoring systems have been developed to detect information in both peripheral joints[3] and spine/sacroiliac joints[4]. While responsiveness of MRI measurements in axial disease with early treatment is well documented[5], data are limited on response of MRI for tenosynovitis, extracapsular information, synovitis, osteitis, and erosive disease.

Additionally, the optimal mode of MRI examination in patients with PsA is debatable. The use of extremity low-field MRI is increasing, but relatively few studies exist on its reproducibility and accuracy in comparison with high-field MRI in PsA.

Our objectives were (1) to assess the responsiveness of MRI measures at multiple timepoints in the first 12 weeks post-antitumor necrosis factor (anti-TNF) therapy initiation in patients with PsA and active dactylitis; and (2) to compare high-field conventional and extremity low-field MRI in the assessment of treatment response in the first 12 weeks of anti-TNF therapy in patients with active PsA.

MATERIALS AND METHODS

Ethics approval was obtained for our study prior to commencement.

Patients with active biologic-naive PsA[6] of the hands or feet and with at least 1 digit exhibiting definite clinical evidence of dactylitis were eligible to be recruited.

Inclusion criteria. Patients were included in our study if they had active PsA, as defined by the ClASsification for Psoriatic ARthritis (CASPAR) criteria,

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Accepted for publication July 27, 2015.

with a swollen joint count (SJC) > 3 and clinical evidence of active dactylitis of at least 1 digit, as judged by the treating clinician. Elevations of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not required for study entry. Patients had been diagnosed with PsA for a minimum of 6 months, and had undertaken previous treatment with at least 2 synthetic disease-modifying antirheumatic drugs (DMARD). All patients were eligible for treatment with a TNF inhibitor under the Medicare Australia Guidelines and were commenced with treatment after the baseline study investigations had been performed. The treating physician chose the type of TNF inhibitor.

Exclusion criteria. All patients with contraindication to MRI or anti-TNF therapy were excluded from our study. Patients with estimated glomerular filtration rate < 38 mls/min were excluded.

MRI variables and study timing. Imaging studies were performed at baseline, 2, 6, and 12 weeks. MRI of the affected hand was undertaken using pre- and postgadolinium (post-GAD) scans. A conventional high-field examination was undertaken and within 48 h a low-field extremity MRI examination was performed. GAD was administered immediately prior to each MRI procedure at 0.1 mmol/kg (Magnevist). The minimum time between high- and low-field MRI was 24 h, and the maximum time was 48 h.

High-field. MRI high-field sequence used a 1.5 Tesla Siemens Magnetom with flex coil with the following variables: coronal and axial T1 sequence TR 420, TE 10.8, slice thickness 2 mm, no gap, matrix 512 × 512; and coronal and sagittal T2 sequence TR 3740 TE 28.6 slice 3 mm, 1 mm gap, matrix 512 × 512. Post-GAD images were fat-suppressed.

Low-field extremity. Low-field extremity imaging was performed using an Artoscan 0.2 Tesla, T1 coronal, and axial TR 1740 TE 18, 256 × 256, slice thickness 3 mm, T2 sagittal TR 4040, TE 28.6, slice thickness 3 mm, matrix 512 × 512. Post-GAD images were not fat-suppressed.

MRI assessment. MRI images were scored by an experienced observer (PB) on 2 separate occasions using the PsA MRI Score (PsAMRIS)[7]. The PsAMRIS assesses tenosynovitis in 3 regions of the digits using a graded scoring system. Five digits are scored over 3 regions providing a potential maximum score of 45. Osteitis, synovitis, periarticular inflammation, and erosions are also scored as described in the PsAMRIS score. For our study, a modified PsAMRIS was used and the images were scored for tenosynovitis, synovitis, and osteitis only. The MRI reader (PB) was blinded to clinical data and therapy.

Statistical analysis. The intraobserver agreement was calculated using average intraclass correlation coefficient, 2-way mixed absolute agreement 95% CI. The average ICC was calculated for high-field scores and low-field scores for tenosynovitis, osteitis, and synovitis.

Clinical data. Clinical data were recorded at baseline and 12 weeks. Clinical data included baseline demographics, dactylitis score[8], ESR, and CRP.

RESULTS

Twelve patients (8 men and 4 women) with active PSA were recruited, all with clinical evidence of dactylitis at baseline. Median age of patients was 43 years (range 27–63) and median weight was 82 kg (range 68–127 kg). The mean disease duration was 8.2 years (SD ± 7.7 yrs). Patients were taking a range of synthetic DMARD at study entry and variable doses of low-dose prednisolone. The details of baseline disease activity scores, SJC/tender joint count, dactylitis scores, and prescribed TNF inhibitor are included with age, weight, and disease duration data in Table 1.

One subject withdrew from the study after consent and baseline clinical data collection (patient 5). Ten patients underwent imaging of the most affected hand and 1 patient of the foot, all with high-field images available. Six patients underwent sequential high-field and low-field MRI examination.

MRI findings. Overall initial scores and score responsiveness were higher for the high-field MRI scores for all inflammation variables.

Tenosynovitis was observed in 9 subjects, more easily visualized on high-field than low-field (Figure 1); 6 of these demonstrated reduction in the tenosynovitis score on high-field MRI at 2 weeks, with 3 patients demonstrating marked improvement (Figure 1, Figure 2, and Figure 3). The improvement on low-field imaging was similar, but less striking.

Synovitis was recorded in 10 subjects on high-field MRI, of which 8 improved at 2 weeks with further improvement through 12 weeks. Low-field imaging demonstrated lower sensitivity to synovitis and osteitis when compared with high-field imaging (Figure 2).

Osteitis was recorded at low level in 7 of 11 patients under high-field MRI, with only 1 patient (patient 8) demonstrating high osteitis scores at baseline and followup (Figure 3). Osteitis was recorded on low-field MRI examination in 1 subject at 1 timepoint.

These improvements were concordant with clinical findings (Table 1). High-field MRI scores were more sensitive to the presence of inflammatory disease features (tenosynovitis, synovitis, osteitis) and showed greater responsiveness to change than low-field MRI scores for these variables (Figures 2 and 3).

Dactylitis scores were recorded at baseline and at 12 weeks. No direct comparison was made between tenosynovitis MRI scores and clinical dactylitis scores, but it was noted that clinical scores moved in the same direction as MRI tenosynovitis scores.

Statistical analysis. The intraobserver ICC for high-field MRI was good for synovitis (ICC 0.88, 95% CI 0.73–0.96), osteitis (ICC 0.62, 95% CI 0.82–0.97), and tenosynovitis (ICC 0.78, 95% CI 0.67–0.93). Similar intraobserver ICC values were noted for low-field MRI synovitis (ICC 0.86, 95% CI 0.63–0.97) and tenosynovitis (ICC 0.89, 95% CI 0.68–0.92). The ICC value for low-field MRI osteitis could not be calculated because the majority of the scores were 0.

DISCUSSION

Our study provides unique data on the clinical use of MRI in demonstrating early responsiveness to treatment with biologic agents. The results highlight dramatic improvement in tenosynovitis, as well as providing the first documented comparison between low- and high-field imaging in PsA.

Of the inflammatory MRI variables studied, tenosynovitis was the most prominent, both in identification and responsiveness. Rapid improvements in high-field and low-field MRI tenosynovitis scores were demonstrated in the majority of subjects at Week 2, with MRI tenosynovitis scores continuing to improve over the 12-week period of treatment in all subjects.

Table 1. Clinical variables.

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5*	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Age, yrs	43	38	37	27	49	49	43	45	42	51	63	42
Sex	M	M	M	M	M	M	F	F	M	F	M	F
Weight, kg	82	92	127	88	91	87	91	—	81	68	70	82.5
PsA duration, yrs	1	2	10	1	6	20	25	13	10	3	6	2
Current DMARD and dose	MTX 20 mg weekly	MTX 25 mg weekly	MTX 20 mg weekly	MTX 20 mg weekly	SSZ 2 g/daily	MTX 25 mg weekly	HCQ 100 mg daily	NIL	NIL	NIL	LEF 20 mg daily, MTX 15 mg weekly	MTX 10 mg weekly, SSZ 2 mg daily
bDMARD	ETN	ADA	ADA	ADA	ADA	ETN	ADA	ADA	IFX	IFX	IFX	IFX
Current PRED	0	0	0	5 mg daily	7.5 mg daily	0	10 mg daily	0	0	0	0	0
TJC baseline/ Week 12, 68 joints	3/0	6/2	4/0	5/0	11	4/2	27/1	13/8	1/0	4/0	4/0	14/17
SJC baseline/ Week 12, 66 joints	9/3	10/4	9/5	4/3	10	8/8	13/7	8/5	22/11	10/1	10/8	5/9
DAS28-ESR baseline/Week 12	3.30/1.55	3.79/2.51	4.04/1.13	2.89/0.51	—	4.75/2.09	4.63/2.1	4.69/3.94	2.99/0.68	4.45	4.36/1.75	3.31/3.66
DAS28-CRP baseline/Week 12	2.53/1.96	3.90/2.23	2.82/0.64	2.40/0.51	—	4.52/2.09	3.87/1.52	3.81/3.17	2.32/0.93	3.51	3.24/0.53	3.81/NIL
Dactylitis scores/ baseline	0	21	41	30	1	52	73	52	90	10	7	40

* One subject withdrew from the study after consent and baseline clinical data collection (patient 5). PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drug; bDMARD: biologic DMARD; PRED: prednisolone; TJC: tender joint count; SJC: swollen joint count; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; NIL: none; LEF: leflunomide; ETN: etanercept; ADA: adalimumab; IFX: infliximab.

Synovitis scoring provided useful information, with synovitis present in the majority of patients and responsiveness demonstrated. Both MRI tenosynovitis and synovitis are therefore useful variables, often corresponding with clinical improvement.

Osteitis scoring was also important, providing adjunctive MRI information that is not available on clinical assessment. Therefore, although osteitis changes were not as dramatic as tenosynovitis, it is important that osteitis remains within any PsA MRI outcome score because this MRI variable provides information regarding disease treatment response that cannot be assessed clinically. It should be noted that the intraobserver agreement for osteitis was lower than synovitis and tenosynovitis. The results, however, still represent good agreement and are consistent with published intrareader studies of osteitis in PsA[9].

High-field MRI was more sensitive and responsive to all 3 MRI inflammation variables. Baseline tenosynovitis scores on high-field MRI were higher, with greater responsiveness demonstrated at 2 weeks and over the 12-week treatment period. These most likely reflect the better resolution of high-field MRI when viewing relatively small structures such as the tendon sheaths of the fingers and toes.

Synovitis scores were more comparable, with only a slight sensitivity and responsiveness advantage conferred by high-field MRI. Of the 6 patients who underwent both high-field and low-field MRI, results were similar with the exception of subject 3, where baseline synovitis scores were markedly higher for high-field MRI scans.

Osteitis MRI scores presented the most obvious discrepancy between high-field and low-field MRI. There was a clear lack of sensitivity and responsiveness of low-field MRI to osteitis in this subject group. Osteitis is scored using short-tau inversion recovery (STIR; T2 fat-suppressed) sequences. The sagittal T2 sequences were used primarily for scoring osteitis, with axial sequences used for clarification. STIR sequences are limited technically on low-field magnets and it is likely that the osteitis scores on low-field MRI represent poor signal-to-noise ratio and poor resolution. This is not an issue only for the low-field MRI used in our study, but an issue for low-field extremity examinations generally.

Low-field extremity imaging may improve as technological advances provide better sequences, but based upon the data in our study, it is difficult to recommend low-field MRI in the evaluation for variables other than synovitis. If MRI is selected as the outcome measure for treatment response, it would seem sensible to choose high-field MRI to allow optimal assessment of tenosynovitis, synovitis, and osteitis.

There are only very few other studies that have used MRI as an outcome measure in PsA. Further, in contrast to the more extensive data on MRI in rheumatoid arthritis (RA), our study is notable for examining MRI response at such early multiple timepoints immediately after treatment initiation.

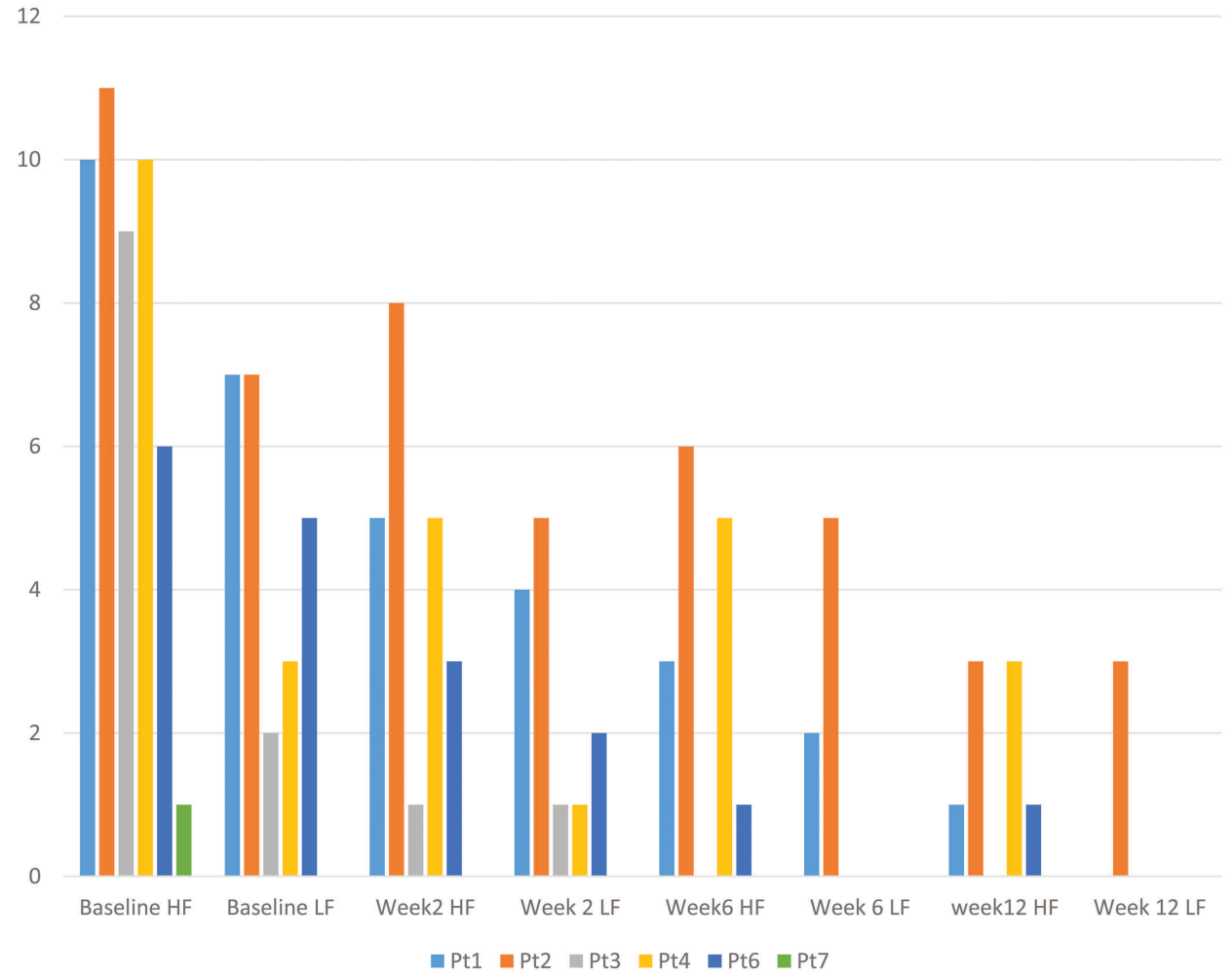

Figure 1. Tenosynovitis HF and LF score comparison. HF: high-field; LF: low-field; Pt: patient.

Our present study reinforces previous trial evidence of MRI responsiveness in PsA.

Anandarajah, *et al* examined 11 patients (active wrist or knee) with PsA treated with adalimumab with the MRI study performed at baseline and after 24 weeks of therapy[10]. In 9 wrists and 2 knees, there was significant improvement in osteitis and joint effusion from baseline to 24 weeks, although it was interesting that a significant amount of osteitis persisted at 24 weeks. This latter finding may reflect the larger joint size in this study, in which osteitis resolved more slowly. Tenosynovitis was not measured in our study.

Marzo-Ortega, *et al*'s group demonstrated a MR imaging response in 18 patients with PsA treated with infliximab (IFX), primarily examining hand osteitis and synovitis at baseline and Week 20[11]. Osteitis was noted in 7 of the 12 subjects with MR wrist (6 completely resolved) and 2 of 6 knees.

Antoni, *et al* examined 10 patients with PsA commencing IFX, describing marked reductions in inflammation on MRI comparing baseline and 10 weeks. Separation of the inflammatory MRI components into categories was not provided in this study, but it was overall noted that MRI was useful for demonstrating response to therapy[12].

These studies were performed prior to the development of the PsAMRIS score, and therefore direct comparisons to our present study are not feasible. Importantly, these studies provide a precedent for the sensitivity and responsiveness of MRI variables in assessing PsA response to therapy and reinforce the findings of our study.

Although no studies exist, to our knowledge, examining high-field MRI and low-field MRI in PsA, a comparison of high-field MRI and extremity low-field MRI has been performed previously in patients with RA. The study examined the agreement between multiple readers for erosions, synovitis, and osteitis in the metacarpophalangeal joints and wrists of subjects with active RA[13]. The agreement for erosions was high for both high-field MRI and low-field MRI (ICC), but the agreement for synovitis (ICC) was lower for low-field MRI and agreement for osteitis (ICC) was moderate at best. This study is important because it identifies

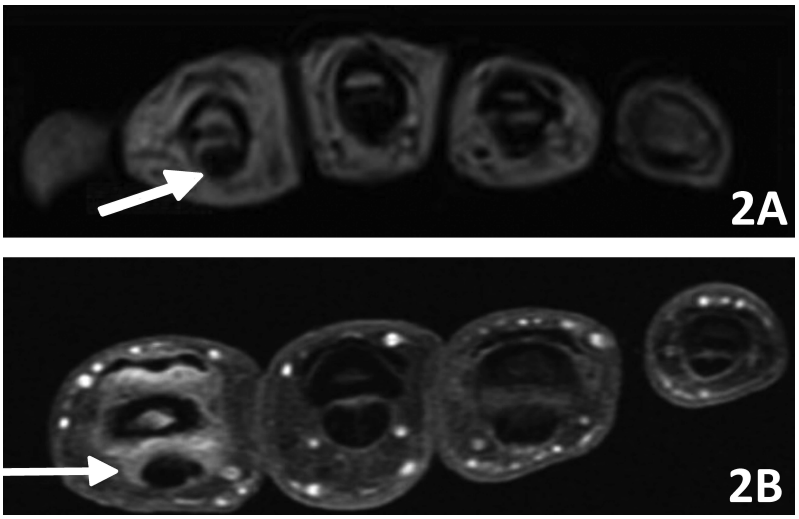

Figure 2. PIP joint tenosynovitis and synovitis (arrow) LF and HF MRI. The images demonstrate the difference in appearance at the same timepoint. The LF images demonstrate low-intensity enhancement, with the HF image showing greater thickness of enhancing synovium and greater intensity of enhancement. (A) Patient 6 baseline post-GAD LF PIP (score 1). (B) Patient 6 baseline GAD HF PIP (score 3). PIP: proximal interphalangeal; LF: low-field; HF: high-field; MRI: magnetic resonance imaging; GAD: gadolinium.

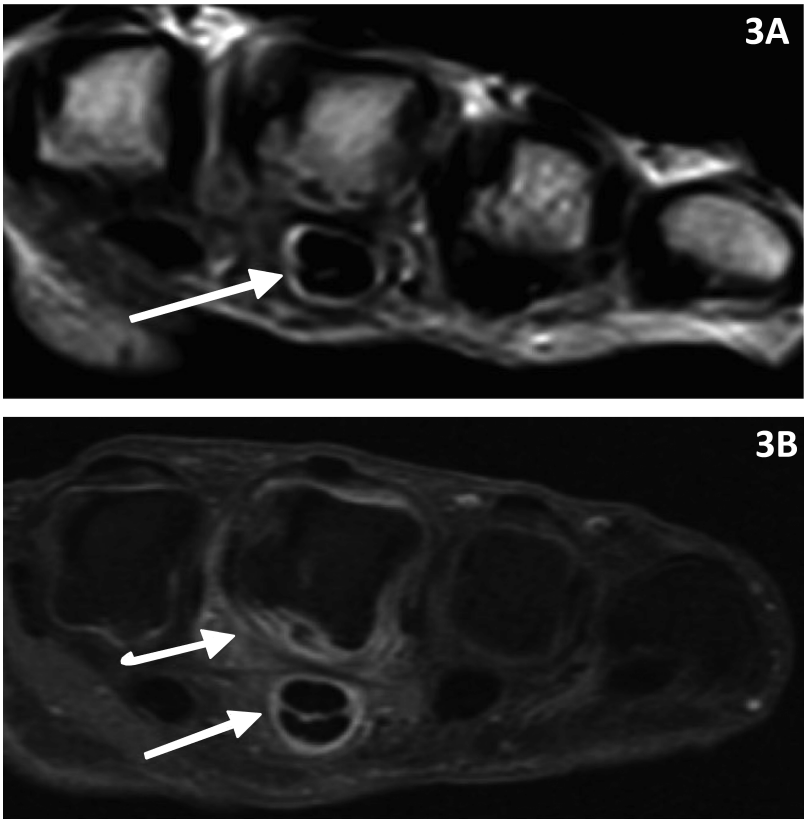

Figure 3. HF and LF MRI baseline images proximal MCP joints. Images show the comparison between images for tenosynovitis third MCP (arrow) and synovitis MCP3. (A) Patient 1 baseline post-GAD LF proximal MCP, T1 post-GAD non–fat-suppressed image (synovitis score 0, tenosynovitis score 1). (B) Patient 1 baseline HF post-GAD proximal MCP, T1 post-GAD fat-suppressed image (synovitis score 1, tenosynovitis score 2). HF: high-field; LF: low-field; MRI: magnetic resonance imaging; MCP: metacarpophalangeal; GAD: gadolinium.

the inherent problems with osteitis scoring on low-field studies, a concept reinforced by our study.

Limitations. There are a number of factors that should be acknowledged as limitations of our study.

The sample size is small; therefore caution should be exercised in generalizing the results of our study to the PsA population. By using our study as a pilot study, it is anticipated that a larger study will be undertaken to confirm the results.

Only a proportion of patients undertook low- and high-field imaging. This was not because of patient comfort, but because of budget constraints such that a subset of patients was randomly assigned to undergo both scans. Our study provides useful comparative data, but any conclusions and recommendations need to take these small numbers into account.

There was only 1 MRI reader in our study; therefore no interobserver agreement scores are available. Previous studies[14] have demonstrated poor interreader agreement for features on low-field MRI. For any future larger study, interreader agreement would improve the strength of the findings.

The high- and low-field images have slightly different variables, dictated by the technical specifications of each magnet. This leads to slight differences in the final axial sections and may affect the readers' appreciation of synovial enhancement post-GAD. In addition, synovial enhancement may show more differences in smaller joints (proximal interphalangeal) compared with larger joints (metacarpophalangeal) — a further factor to be considered when comparing low- and high-field studies. Accordingly, the authors do not advocate the abandonment of low-field MR imaging in PsA, but recommend that these factors should be taken into account when interpreting the results of our study.

A further technical limitation was the level of fat suppression on T1-weighted images post-GAD. The high-field images included fat saturation post-GAD. Technical limitations of the type of low-field magnet used in our study meant that fat suppression was not reliable, and thus it was decided not to pursue fat suppression in the low-field studies. This would have created a potential source of difference in scores between the high- and low-field studies for the synovitis and tenosynovitis variables.

PsA is a heterogeneous disorder and it must be recognized that these small cohort results may not be generalizable to all patients with PsA or even all with dactylitis.

Even with these limitations, however, our study provides important objective imaging data in patients with active PsA and their response to anti-TNF therapy.

Notwithstanding the limitations of our study, MRI demonstrated responsiveness in the first 12 weeks after biologic therapy initiation for MRI tenosynovitis, synovitis, and osteitis. MRI tenosynovitis exhibited the greatest use, with excellent sensitivity and responsiveness. MRI improvement was noted 2 weeks after therapy initiation.

High-field MRI demonstrated greater sensitivity and responsiveness compared with low-field for all variables. Osteitis was the variable with the greatest scoring discrepancy between the hand low-field extremity MRI.

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