# Systematic Review of MRI, Ultrasound, and Scintigraphy as Outcome Measures for Structural Pathology in Interventional Therapeutic Studies of Knee Arthritis: Focus on Responsiveness

HELEN I. KEEN, PHILIP J. MEASE, CLIFTON O. BINGHAM III, JON T. GILES, GURJIT KAELEY, and PHILIP G. CONAGHAN

***ABSTRACT***. ***Objective.*** Validated imaging outcome tools to assess response to therapies in a single joint are required. Our aim was to review the published literature to ascertain the responsiveness of novel imaging techniques as outcome measures in interventional therapeutic studies of knee arthritis.

***Methods.*** An Ovid Medline search was performed for original articles in English that used imaging techniques to assess response at the knee joint to therapy in osteoarthritis, rheumatoid arthritis, and psoriatic arthritis. Changes in response to therapy were assessed with regard to both internal and external responsiveness.

***Results.*** In the studies that presented appropriate statistical data to allow responsiveness to be assessed, MRI was generally found to be internally responsive to pathologies imaged, and externally responsive, referenced against both other imaging modalities and biochemical biomarkers of arthritis. Ultrasonography was found to demonstrate internal responsiveness with regard to synovial thickness, effusion size, and popliteal cyst size. External responsiveness was demonstrated against several referenced health status measures. Scintigraphy was found to be externally responsive in the majority of studies, with internal responsiveness demonstrated in 1 study.

***Conclusion.*** While the imaging techniques appear to be responsive from the data we present, further inspection reveals that interpreting the responsiveness of imaging techniques was difficult, largely because of a lack of standardization of image acquisition, definitions of pathology, and scoring systems. Refined pathological definitions and scoring systems are required to enable the development of valid and responsive tools for interventional clinical trials. (First Release Oct 1 2010; J Rheumatol 2011;38:142–54; doi:10.3899/jrheum.100377)

*Key Indexing Terms:*
ULTRASONOGRAPHY MAGNETIC RESONANCE IMAGING SCINTIGRAPHY
OMERACT KNEE ARTHRITIS IMAGING SYSTEMATIC REVIEW

Assessment of the efficacy of therapies in the clinical trial setting relies on the use of outcome tools to define improvement. Additionally in the clinical setting, application of objective measurement tools to guide management results in better outcomes[1]. However, the development and application of such tools in clinical trials in rheumatology is relatively recent, and for many rheumatic conditions, appropriately validated tools are not currently available. Improvement of outcome measurement in rheumatology clinical trials is the focus of the Outcome Measures in Rheumatology Clinical Trials group (OMERACT), an informal network of working groups. OMERACT's agenda is to establish validated, objective, and feasible measurement tools that demonstrate truth, discrimination, and feasibility (the OMERACT filter)[2]. Application of this filter allows an outcome tool to be assessed regarding metric properties such as face, content, construct, and criterion validity, reproducibility, and responsiveness.

Many of the validated outcome measures in rheumatology clinical trials [such as the Disease Activity Score (DAS) and the American College of Rheumatology (ACR) responder criteria] consist of a composite of domains assessing systemic response to therapies. These outcome tools have

*From the School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; Seattle Rheumatology, Seattle, Washington; Johns Hopkins University, Rheumatology, Baltimore, Maryland; the University of Florida College of Medicine, Jacksonville, Florida, USA; the Section of Musculoskeletal Disease, University of Leeds; and the National Institute for Health Research (NIHR), Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK.*

*H.I. Keen, MBBS, FRACP, School of Medicine and Pharmacology, University of Western Australia; P.J. Mease, MD, Seattle Rheumatology; C.O. Bingham III, MD; J.T. Giles, MD, Johns Hopkins University, Rheumatology; G. Kaeley, MBBS, University of Florida College of Medicine; P.G. Conaghan, MBBS, PhD, FRACP, FRCP, Section of Musculoskeletal Disease, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit.*

*Address correspondence to Prof. P. Conaghan, Section of Musculoskeletal Disease, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK. E-mail: p.conaghan@leeds.ac.uk*

*Accepted for publication August 12, 2010.*

been invaluable in establishing the efficacy of pharmacotherapeutics in rheumatology, and aided the advancement of therapies and treatment paradigms, such that the treatment and outcome of many rheumatic conditions is now much improved. However, it has been recognized that these outcome tools may have limited use in evaluating outcomes at the single-joint level, for example when assessing localized intraarticular (IA) therapy[3] in the setting of systemic arthritis with only a few refractory joints, and in pauciarticular processes such as monoarthritis. Validated, objective outcome tools are required in order to move the field of rheumatology forward in these situations.

Recently, the OMERACT Single Joint Working Group reviewed publications evaluating clinical, radiographic, and functional assessments of single joints, focusing on the knee[3]. Our aim was to examine novel, nonradiographic imaging techniques and to systematically assess the published literature for evidence of their responsiveness as outcome tools for arthritis of the knee joint.

## MATERIALS AND METHODS

A systematic literature review was undertaken with the objective of identifying studies that used imaging outcome tools to measure response to interventional therapies in arthritis of the knee joint, limited to cohorts with a diagnosis of rheumatoid arthritis (RA), osteoarthritis (OA), or psoriatic arthritis (PsA). Therefore the inclusion criteria were published studies in English, assessing humans *in vivo*, comparing imaging of structural tissue pathology of the knee joint before and after a specific therapeutic intervention. Studies were excluded if they measured only biomechanical pathology, such as abnormal joint alignment. Studies were also excluded if they imaged multiple joints, and data regarding the knee specifically could not be extracted, or they were not the first report. The quality of the trial methodology or reporting was not an inclusion or exclusion criterion. An Ovid Medline search was conducted to identify articles published between 1950 and May 2010 using such search terms as rheumatoid arthritis; arthritis; osteoarthritis, hip; osteoarthritis; osteoarthritis, knee; psoriatic arthritis; ultrasonography, Doppler; magnetic resonance imaging; whole body imaging; diagnostic imaging; radionuclide imaging; three-dimensional; scintigraphy; tomography; x-ray computed or computer tomography; and optical coherence tomography. The titles and abstracts were reviewed to exclude duplicates and identify those articles meeting inclusion criteria. The articles were reviewed and data extracted and inserted into a template based on the previous work of the OMERACT Single Joint Assessment Working Group, but modified for our review[3]. The extracted data addressed aspects of study design and size, imaging modality and specifications, and pathology imaged, including definitions, scoring system, and change in response to interventional therapies to assess responsiveness, including the statistical method used.

For the purpose of this review, we focused on internal responsiveness and external responsiveness. Internal responsiveness was defined as the ability of an outcome tool to demonstrate temporal changes in response to therapy. Statistical tests considered appropriate for determining responsiveness included the paired t test, standardized response mean (SRM), standardized effect size (SES), and Gyatt's responsiveness index (GRI)[4]. For our review, if studies used SRM, SEM, or GRI to assess responsiveness, the tool was considered responsive if the result was $\geq 0.2$ (considered a small response)[4]. External responsiveness is the extent to which changes in an outcome tool correlate with other referenced measurements. Appropriate statistical tests to assess external responsiveness include the receiver-operating characteristic method, correlation coefficients, and regression analysis[4].

## RESULTS

The Medline search identified 5824 published articles, 77 of which were duplicates. Articles having the word "knee" in the title, abstract, or notes numbered 1148, and these were reviewed to determine whether they met the inclusion criteria. A further 6 articles were identified by consulting experts and examining reference lists of relevant review articles. We included 49 articles in our review. Reasons for the exclusion of articles appear in Figure 1.

Individual study designs, including the disease studied, cohort size, and imaging techniques used, are summarized in Table 1. Therapies studied were predominantly IA, including corticosteroids, radiosynovectomy, or hyaluronic acid; oral therapies included methotrexate, leflunomide, corticosteroids, or nonsteroidal antiinflammatory drugs; parenteral therapies included infliximab, etanercept, and corticosteroids; surgery ranged from synovectomy to wedge osteotomy; and physical therapy included repetitive short-wave diathermy.

Scoring systems for knee arthritis were examined in magnetic resonance imaging (MRI) studies (Table 2), ultrasound studies (Table 3), scintigraphic studies (Table 4), and 1 thermography study; no studies were included that used computed tomography or optical coherence tomography.

MRI studies generally provided adequate details of the machine settings, including slice thickness (Table 2). Changes in machine settings and the use of contrast agents occurred in relation to when the study was undertaken. Joint positioning was rarely described in MRI studies. Descriptions of the imaging appearance of pathology in MRI studies were rarely given. Scoring systems varied greatly; some studies scored individual pathologies. Additionally, some studies used software to calculate scores based on cross-sectional area or volume of the imaged tissue or pathology, tissue thickness, or tissue interface, while others used physician readers to score according to dichotomous or semiquantitative systems. Internal responsiveness of MRI to changes in the following pathologies was found in at least 1 article: synovial thickness, enhancement, effusion, bone marrow lesions, cartilage volume and morphology, osteophytes, and quadriceps volume. External responsiveness was rarely studied, but MRI demonstrated external responsiveness in 2 of the articles, referenced against both other imaging modalities and biochemical biomarkers of arthritis.

The ultrasound studies (Table 3) demonstrated a large amount of heterogeneity. While most studies adequately described the machine and machine settings, there was variability in the settings, for example the pulse repetition frequency, wall filter, and Doppler settings (when used) were not uniform. The position of the knee during image acquisition was specified in more than half the studies, although the knee position again was not uniform. Knee positioning included flexion, neutral, and extension, with 1 author using

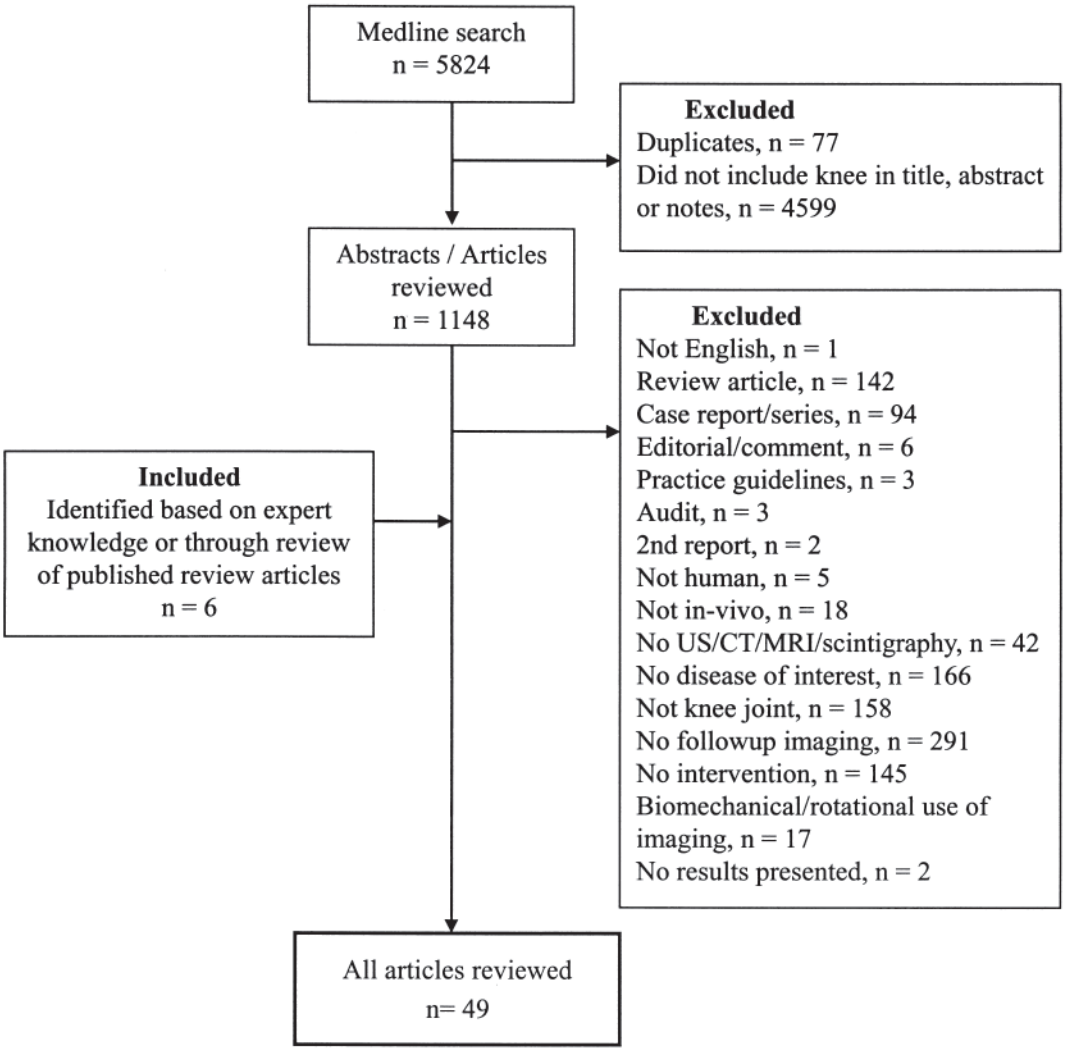


*Figure 1*. Search strategy and reasons for excluding trials from the review — assesses external responsiveness only.

an extended knee with contracted quadriceps in 1 article, and relaxed quadriceps in another. The definition of the imaging appearance of pathology was described in fewer than half the articles, and was seemingly unrelated to the year of publication. Definitions were not uniform, nor were they in keeping with OMERACT definitions of ultrasound-defined pathology[5]. Scoring systems varied between being descriptive of morphology, dichotomous, semiquantitative (0–3 scale), quantitative measurements (such as tissue thickness), or summative quantitative systems (adding regional tissue thickness measurements). Ultrasonography was found to demonstrate internal responsiveness with regard to synovial thickness, effusion size, and popliteal cyst size. External responsiveness was demonstrated against several referenced health status measures.

Scintigraphic studies are presented in Table 4. Technetium was the most common labeling agent, but other agents were used. Almost a third of articles did not describe the scoring systems, and when specified, they included semiquantitative systems or computer-generated scoring systems. Scintigraphy was found to be externally responsive in the majority of articles, but internal responsiveness was examined in only 1 article.

## DISCUSSION

In our systematic review we identified only 49 articles using MRI, ultrasound, and scintigraphy to assess change in response to therapies in arthritis of the knee joint. Studies assessing the responsiveness of MRI were the most prevalent, and they reported MRI to be both internally and externally responsive to many pathological features of knee arthritis, including synovial thickness, enhancement, effusion, bone marrow lesions, cartilage volume and morphology, osteophytes, and quadriceps volume. Three reports assessed the internal responsiveness of ultrasound, finding it responsive to changes in synovial thickness, effusion, and

*Table 1.* Summary of studies identified meeting inclusion criteria, including study design, disease studied, imaging modality, and route of therapy.

| Study | Study Design | | | | No. Patients Disease | | | Imaging | | | | Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Powered | Controlled | Randomized | Blinded | RA | PsA | OA | MRI | US | Sc | Th | |
| Acebes[8] 2006 | — | — | — | — | | | 30 | | Y | | | IA ST |
| Al-Janabi[9] 1988 | — | — | — | — | 7 | | | | | Y | | IA ST |
| Al-Janabi[10]1992 | — | — | — | Single | 11 | | | | | Y | | IA ST |
| Alonso-Ruiz[11] 1998 | — | — | — | — | 10 | | | Y | | | | IA HA or placebo |
| Bagge[12] 1996 | — | Y | Y | Single | 11 | | | Y | | | | IA IgG or IA saline |
| Batalov[13] 1999 | — | — | — | — | 24 | | | | Y | | | Arthroscopic synovectomy |
| Beckers[14] 2006 | — | — | — | — | 16 | | | Y | Y | Y | | Steroids or NSAID |
| Brandt[15] 2006 | — | — | — | Single | | | 30 | Y | | | | NSAID or paracetamol |
| Creamer[16] 1994 | — | Y | Y | Single | | | 12 | Y | | Y | | IA HA |
| Creamer[17] 1997 | — | Y | — | Single | 16 | | | Y | | | | Aspiration and IA ST ± yttrium synovectomy |
| Cubukcu[18] 2005 | — | Y | Y | — | | | 30 | Y | | | | IA HA or placebo |
| De Bois[19] 1993 | — | — | — | Single | 7 | | | | | Y | | IA ST |
| Fiocco[20] 1996 | — | Y | — | Single | 12 | 11 | | | Y | | | Surgical synovectomy |
| Fiocco[21] 2005 | — | — | — | — | 12 | 8 | | | Y | | | SC etanercept 25 mg twice weekly |
| Forslind[22] 2004 | — | — | — | Single | 20 | | | Y | | | | Oral prednisolone and/or various DMARD* |
| Arzu Gencoglu[23] 2003 | — | — | — | — | 23 | | | | | Y | | Y-90 silicate radionuclide synovectomy |
| Arzu Gencoglu[24] 2002 | — | — | — | — | 15 | | | | | Y | | Sulindac |
| Glaser[25] 2007 | — | — | — | — | | | 21 | Y | | | | Autologous chondrocyte implant |
| Hunter[26] 2006 | Y | Y | Y | Double | | | 150 | Y | | | | Oral experimental therapy (NI-15713) |
| Iagnocco[27] 2006 | — | — | — | Single | 10 | 13 | | | Y | | | IA MTX weekly for 8 wks, then oral MTX |
| Jan[28] 2006 | — | Y | — | — | | | 36 | | Y | | | Repetitive shortwave diathermy |
| Jones[29] 1991 | — | — | — | Single | 13 | | 9 | | | Y | | IA ST |
| Kroner[30] 2007 | — | — | — | Single | | | 20 | Y | | | | Lateral closing wedge osteotomy |
| Lee[31] 2003 | — | — | — | — | 14 | | | Y | | | | IA holium-166-chitosan complex |
| Leitch[32] 1996 | — | — | — | Single | 6 | | | Y | | | | Arthrocentesis and IA ST |
| Marzo-Ortega[33] 2007 | — | — | — | Single | 6 | | | Y | | | | Infliximab |
| Mizner[34] 2005 | — | — | — | — | 20 | | | Y | | | | Tricompartmental knee arthroplasty |
| Moore[35] 1975 | — | — | — | — | 17 | | | | Y | | | IA steroid and local anesthetic or local anesthetic or synovectomy† |
| Newman[36] 1996 | — | — | — | — | 5 | 1 | | | Y | | | Arthrocentesis and IA ST |
| Ostergaard[37] 1996 | — | — | — | — | 15 | 2 | 1 | Y | | | | Aspirate to dryness and IA methylprednisolone 80 mg* |
| Ozturk[38] 2006 | — | Y | Y | Single | 47 | | | Y | | | | IA HA and IA steroid or IA HA |
| Reece[39] 2002 | — | Y | Y | Double | 39 | | | Y | | | | MTX or leflunomide |
| Rubaltelli[40] 1994 | — | — | — | — | 12 | 13 | | | Y | | | Arthroscopic synovectomy |
| Salaffi[41] 2004 | — | — | — | Single | 18 | | | | Y | | | IA ST |
| Sharma[42] 1999 | — | Y | Y | Double | | | 49 | Y | | | | Nimesulide or piroxicam |
| Shin[43] 2007 | — | Y | — | Single | 16 | | | Y | | | | IA 188 Re-tin colloid 3 doses |
| Shio[44] 2006 | — | — | — | — | 10 | | | | Y | | | IV Infliximab |
| Soroa[45] 2005 | — | Y | — | Single | 12 | | | | | Y | | IA steroid or IA P-32 Colloid |
| Tannenbaum[46] 1987 | — | — | — | Single | 15 | | | | | Y | | Sulindac |
| Uematsu[47] 1979 | — | — | — | — | 14 | | | | | Y | | High tibial osteotomy |
| Van Holsbeeck[48] 1988 | — | — | — | — | 20 | | | | Y | Y | Y | IA ST |
| Veale[49] 1999 | Y | Y | Y | Single | 13 | | | Y | | | | Arthroscopy and biopsy followed by IA anti-CD4 |

*Table 1.* Continued.

| Study | Study Design | | | | No. Patients Disease | | | Imaging | | | | Therapy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Powered | Controlled | Randomized | Blinded | RA | PsA | OA | MRI | US | Sc | Th | |
| Wluka[50] 2002 | Y | Y | Y | Double | | | 136 | Y | | | | Vitamin E |
| Youssef[51] 1996 | — | — | — | — | 9 | | | | | Y | | IV methylprednisolone |
| Song[52] 2009 | — | Y | Y | Double | | | 41 | Y | Y | | | IA bradykinin receptor 2 antagonist |
| Raynauld[53] 2009 | Y | Y | Y | Double | | | 355 | Y | | | | Licofelone or naproxen |
| Raynauld[54] 2008 | U | U | U | U | | | 107 | Y | | | | Bisphosphonate or NSAID or COX-2 inhibitor |
| Raynauld[55] 2008 | Y | Y | Y | Double | | | 355 | Y | | | | Licofelone or naproxen |
| Anandacoomarasamy[56] 2008 | Y | — | — | — | | | 19 | Y | | | | IA Hylan |

* Variety of oral therapies also used. † One subject had surgical therapy. RA: rheumatoid arthritis; PsA: psoriatic arthritis; OA: osteoarthritis; MRI: magnetic resonance imaging; US: ultrasonography; Sc: scintigraphy; Th: thermography; IA: intraarticular; IV: intravenous; HA: hyaluronic acid; ST: corticosteroid; P: parenteral; PH: physical; SC: subcutaneous; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; COX-2: cyclooxygenase-2; U: unknown; Y: Yes.

popliteal cysts size, with marked variability in the definitions of pathology, image acquisition, and scoring system used. The external responsiveness of ultrasonography was also assessed in 4 reports, finding correlations between ultrasound and externally referenced health status measures. Scintigraphy was found to be externally responsive in the majority of articles, with little investigation into its internal responsiveness.

While the imaging techniques appear to be responsive from the data, further inspection reveals that interpreting the responsiveness of imaging techniques was difficult for many reasons. Challenges in assessing the responsiveness of these imaging techniques focused on the image acquisition and analysis. These included a lack of standardization in acquiring images, a lack of standard definitions of pathology, and a lack of standardized scoring systems. It is inevitable that variability will be associated with imaging studies, as advances in technology result in improvements in machine capabilities and techniques, such as the addition of contrast agents. Additionally, scientific progress, such as advances by OMERACT in creating standard definitions of ultrasound imaged pathology, will influence study methodology and publication style. However, based on the current published literature, it is difficult to identify which imaging techniques fulfill the OMERACT filter with regard to discrimination; and the variability demonstrated in machine settings, image acquisition, definitions of pathology, and scoring systems makes comparisons between articles difficult.

This systematic review has limitations. We focused on 1 joint only (the knee), and importantly we excluded observational studies in favor of those looking at interventional effects. Other groups have looked at responsiveness for MRI cartilage measures in OA knee using longitudinal studies[6,7]. Adequately assessing the responsiveness of a tool is dependent on using effective therapies. If a study uses a therapy that is unable to bring about change in health status, then the responsiveness of the tool may be underestimated[4]. Similarly, if a study examines a subgroup that is likely to respond excessively well to an outcome, then the responsiveness of the tool is likely to be overestimated. In our review, no analysis of the effectiveness of the intervention, or the likelihood of the treatment cohort to respond, was made. We were only able to assess the responsiveness of MRI, ultrasound, and scintigraphy regarding studies that reported appropriate measures and it was not possible to calculate SRM from many studies.

The imaging modalities we studied are well placed to be used as objective outcome tools in knee arthritis, but more work is required before these modalities can be considered to fulfill the OMERACT filter of truth, discrimination, and feasibility as outcomes tools in both inflammatory arthritis and OA of the knee. Our review has identified insufficiencies in the principles of discrimination. Our review highlights greater issues that need further consideration before outcome tools for clinical trials evaluating therapies at the knee joint can be developed. First, whether a generic (as distinct from disease-specific) outcome tool is needed must be carefully considered. Second, the pathologies to be imaged need to be identified and their imaging appearances defined. Image acquisition must be standardized for each imaging modality, including the machine setting, fields of view, and joint positions, although it is recognized that this will change with emerging technology. We recommend that research focus on these issues, and on developing international consensus guidelines for the use of modern imaging techniques in rheumatology clinical trials. Once these basic considerations have been addressed, further work assessing the performance metrics of the tool can be undertaken. Until validated responsive imaging outcome tools are developed, the ability to rigorously examine the mode of action and efficacy of therapies on single joints *in vivo* is limited.

*Table 2*. Summary of the magnetic resonance imaging (MRI) studies, including pathology scoring system, and responsiveness.

| Study | RA | PsA | OA | Gd-DTPA | Pathology | Scoring System | Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Alonso-Ruiz[11] | Y | | | Y | Synovium | Synovial thickness (mm) in supra patella pouch<br>Synovial enhancement (%) software | MRI demonstrated a reduction in synovial thickness, at all timepoints<br>Enhancement significantly reduced at followup from baseline | Y | Y | N | U/A |
| Anandaco-omarasamy[56] | | | Y | | Cartilage volume<br>Cartilage defects | Manual segmentation<br>Semiquantitative score 0–4 | No change in cartilage volume of cartilage defect scores | N | N | N | U/A |
| Bagge[12] | Y | | | Y | Synovitis/pannus<br>Hydrops<br>Baker cyst | Unclear | MRI improved in 2/6 receiving IgG, worsened in 1/6. MRI findings improved in 3/5 receiving saline, and worsened in none | N | U/A | N | U/A |
| Beckers[14] | Y | | | Y | Synovitis | Relative enhancement, and rate of early enhancement and static enhancement | At 4 weeks, significant correlation between changes in PET, MRI, CRP, MMP-3, but not ultrasound | | | Y | Y |
| Brandt[15] | | | Y | Y | Synovitis effusion | Computer-aided assessment of volume | Both treatment groups showed a reduction in mean total effusion after therapy ($p < 0.009$ and $p < 0.01$) | Y | Y | N | U/A |
| Creamer[16] | | | Y | | Pannus, effusion, enhancement | Pannus, effusion and enhancement score with both semiquantitative scoring system (0–2) and computer-aided quantification | No MRI difference between baseline and followup | N | U/A | N | U/A |
| Creamer[57] | | | Y | | Effusion<br>Synovial thickening | Change in effusion volume<br>Synovial thickening unspecified | IA ST cohort: change in fluid volume calculated by computer strongly correlated with aspirated volume.<br>Significant reduction in MRI synovial volume and enhancement by both methods at 1 week. No change in pannus by either method.<br>Synovectomy cohort: there was no change in pannus, effusion, or enhancement by MRI by either scoring system | N | U/A | N | U/A |
| Cubukcu[18] | | | Y | Y | Patella cartilage | Modified Shahriaree classification (0–4) | Significant improvement in cartilage grade in the treatment group, but not the placebo group. No change in other MRI features. | N | U/A | N | U/A |
| Forslind[22] | Y | | | Y | Synovitis<br>Erosions<br>Edema | Sum of 0–3 in 4 compartments<br>Number and location<br>Presence | All bar 1 subject with baseline synovitis had synovitis at followup.<br>No. of subjects with erosions increased from 5 to 11 at followup.<br>No. of subjects with edema progressed with time from 1 to 4 | N | U/A | N | U/A |
| Glaser[25] | | | Y | | Cartilage | Software to determine volume, mean and local cartilage thickness, cartilage bone interface, and volume normalized to size of cartilage | A mean increase in cartilage volume and thickness of 6% was observed in the treatment group, $p < 0.001$ | Y | Y | N | U/A |

*Table 2.* Continued.

| Study | RA | PsA | OA | Gd-DTPA | Pathology | Scoring System | Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hunter[26] | | | Y | | Cartilage volume<br>Bone edema, attrition, cysts<br>Osteophytes<br>Synovial cavity distension | WORMS | Small changes in scores for cartilage morphology, synovitis, and osteophytes, with a trend toward differences between treatment and placebo groups | Y | Y | N | U/A |
| Kroner[30] | | | Y | | Bone marrow edema | Bone marrow edema volume calculated, and and regions in medial tibial and femoral compartments summed | Mean size of bone marrow edema lesion decreased from 4.21 $cm^3$ to 1.2 $cm^3$ at 1 year, and was maintained at 7 years. JOA score improved at 1 year but decreased slightly at 7 years | Y | Y | N | U/A |
| Lee[31] | Y | | | Y | Synovial enhancement<br>Synovial thickness<br>Baker cyst<br>Erosions | Software (scion image) calculated volume<br>Synovial thickness measured in SPP<br>Effusion calculated using scion image volume in $mm^3$<br>Baker cyst volume<br>Number of erosions | Synovial enhancement and thickness and Baker cysts volume did not significantly decrease, although effusion did. Erosion scores did not change | Y | Y (effusion only) | Y | N |
| Leitch[32] | Y | | | Y | Effusion<br>Synovium | Effusions scored 0–4<br>Synovial thickness measured in mm | Reduction in effusion volume by semiquantitative score in 4 patients.<br>Reduction in synovial thickness, most striking in those with thickest synovium at baseline, the rest had minimal changes in fluid and synovium | N | U/A | N | U/A |
| Marzo-Ortega[33] | | Y | | Y | Bone marrow edema<br>Synovium | Semiquantitative score 0–3 for bone marrow edema<br>Synovial enhancement volume calculated using software | Bone edema resolved in 1, was unchanged in 1.<br>Reduction in synovial enhancement volumes in 4/6 | N | U/A | N | U/A |
| Mizner[34] | | | Y | | Quads volume | Cross-sectional area | Quads volume decreased as did strength and voluntary activation | Internal | Y | Y | Y |
| Ostergaard[37] | Y | Y | Y | Y | Synovitis | Relative enhancement, rate of early enhancement | All knees demonstrated a decrease in rate of early enhancement at 7 days. All knees that relapsed demonstrated an increase in rate of early enhancement at relapse. Knees in clinical remission at day 30 have a decrease in rate of early enhancement compared to baseline, but most of these had increased since day 7. | N | U/A | N | U/A |
| Ozturk[38] | | | Y | | Marrow edema<br>Cartilage thinning<br>Baker cyst<br>Effusion<br>Subchondral cysts<br>Erosions | Global score 1–8 (w/edema)<br>Cartilage thinning<br>Baker cyst<br>Effusion<br>Subchondral cysts<br>Erosions | No significant progression in MRI scores for either group | N | U/N | N | U/A |

*Table 2.* Continued.

| Study | RA | PsA | OA | Gd-DTPA | Pathology | Scoring System | Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Raynauld[54] | | | Y | | Subchondral bone changes<br>Meniscal lesions | Identified as edema or cyst, then measured in mm<br>Described elsewhere | No change in bone lesions<br>Unclear | Y (bone lesions only) | N | N | U/A |
| Raynauld[55] | | | Y | | Cartilage volume and mean thickness<br>Meniscal extrusion | 3-D coordinate system and Euclidean distance between bone to cartilage interface and cartilage to soft tissue interface<br>Extrusion scored on 0–2 semiquantitative scale | Less cartilage loss in the licofelone group | N | U/A | N | U/A |
| Raynauld[53] | | | Y | | Cartilage volume | Unclear | Significantly less cartilage loss in the licofelone group | Y | Y | N | U/A |
| Reece[39] | Y | | | Y | Synovial inflammation | The rate of enhancement and maximal enhancement | Significant improvement in rate of enhancement in leflunomide group compared to MTX group. No difference between the groups with regard to a decrease in maximal enhancement that improved with therapy | N | U/A | N | U/A |
| Sharma[42] | | | Y | | Cartilage thickness | Cartilage thickness (0–4) | No change over 24 weeks in cartilage grades. OA Severity Index, tenderness and swelling significantly improved at 8 and 24 weeks in the patients that completed the timepoints (n = 49 and 11), with no difference between treatment groups | U/C | U/A | N | U/A |
| Shin[43] | Y | | | Y | Synovitis<br>Effusion | Change in synovitis scored from –2 to 2, Sum of mm in SPP and IPP in the sagittal plane<br>Change in effusions scored from –2 to 2 | Synovial thickening improved in treated knee in 87.5% and effusion decreased in 43.7%. Synovial thickness decreased at 6 months (by 1.68 mm), but slightly increased in control knees (–0.18 mm) | N | U/A | N | U/A |
| Song[52] | | | Y | Y | Contrast medium enhancement<br>Effusion | Score 0–3 based on measurement in mm (< 5 mm, < 8 mm, < 11 mm, ≥ 11 mm)<br>Semiquantitative score 0–3 | Reduction in effusion in the high-dose treatment group. At followup, MRI correlated with ultrasound | U/C | U/A | N | U/A |
| Veale[49] | Y | | | Y | Synovitis | Synovial maximal rate of enhancement, and maximal enhancement | MRI demonstrated a trend toward a dose effect for improvement in synovial measurements with therapy (nonsignificant) | N | U/A | N | U/A |
| Wluka[50] | | | Y | | Cartilage volume | Unclear | Loss of cartilage from baseline (similar volume loss in both cohorts) | N | U/A | N | U/A |

RA: rheumatoid arthritis; PsA: psoriatic arthritis; OA: osteoarthritis; U/A: unable to assess; PET: positron emission tomography; CRP: C-reactive protein; MMP: matrix metalloprotease; IA ST: intraarticular corticosteroid; WORMS: whole-organ magnetic resonance imaging score; JOA: Japanese Orthopaedic Association; SPP: suprapatellar pouch; IPP: intrapatellar pouch. Y: yes; N: no.

*Table 3*. Summary of the ultrasound studies, including pathology studied, scoring system used, and responsiveness.

| Study | Disease RA | Disease PsA | Disease OA | Knee Position | Regions Imaged | Definition of Pathology Imaged | Definition of Scoring System Used | Description of Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acebes[8] | | | Y | | Popliteal fossa | | Popliteal cyst synovial wall thickness in mm, popliteal cyst wall area using built-in software | Popliteal cyst size and wall thickness decreased after therapy | Y | Y | Y | Y |
| Batalov[13] | Y | | | | SPP | | Maximal synovial thickening in the SPP (anterior and posterior wall) in the AP diameter in mm. Effusion depth assessed as the maximal AP thickness of the suprapatella sac in mm | Mean ultrasound synovitis thickness and effusion significantly reduced at 3 and 12 months posttherapy | N | U/A | N | U/A |
| Song[52] | | | Y | | SPP, LR | | Effusion 0–3 based on measurements in mm, synovial hypertrophy 0–3 based on measurements in mm; PD semiquantitative scale 0–3 | No changes in the treatment group. At followup, ultrasound demonstrated correlations with symptoms and MRI | U/C | U/A | N | U/A |
| Beckers[14] | Y | | | Extended | SPP, MR LR (a) | Y** | Contrast enhancement semiquantitative score 0–3 using slope values synovial thickening present when the sum of the anterior and posterior walls of the pouch measured > 1 mm. Power Doppler signal assessed on semi-quantitative scale 0–3 | At 4 weeks, significant correlation between changes in PET, MRI, CRP, and MMP-3, but not ultrasound | N | N | Y | N |
| Fiocco[20] | Y | | | Extended (d) | SPP, MR LR (b) | Y* | Synovial thickening assessed, as highest score of the SPP or MR or LR as assessed in mm. Pouch thickness measured in mm, then graded 0–3, morphology noted | Ultrasound synovial thickness and effusion decreased significantly at 2 and 12 months. Morphological pattern did not change after synovectomy | Y | Y | N | U/A |
| Fiocco[21] | Y | Y | | Extended (e) | SPP, MR LR (b) | Y* | Synovial thickening assessed, as highest score of the SPP or MR or LR assessed in mm. Power Doppler graded from 0–3 | Ultrasound variables decreased at 12 months, as did all clinical measures of disease activity (except global health score) | N | U/A | N | U/A |
| Iagnocco[27] | Y | Y | | Neutral | SPP | Y | Synovium of posterior wall of SPP present or absent (> 3 mm considered present) Popliteal cyst present or absent, effusion present or absent | At 3 months, only the PD score was significantly decreased. Synovial thickness decreased by week and further by week 17 (5.5 mm, 4.83 mm, 4.65 mm) Number with effusion decreased from 12 to 4 at week 9, Baker cysts decreased from 5 to 1 (although not significant) | Y | Y | N | U/A |
| Jan[28] | | | Y | 30° flexion | SPP, LR MR | | Sac thickness, a summation of measurements in mm in the SPP, LR, MR | Decrease in sac thickness in the treatment group, but not in control group | N | U/A | N | U/A |

*Table 3.* Continued.

| Study | Disease RA | PsA | OA | Knee Position | Regions Imaged | Definition of Pathology Imaged | Definition of Scoring System Used | Description of Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moore[35] | Y | | | | Popliteal fossa | | Popliteal cyst presence | Effusion and cysts persisted despite clinical improvement in the majority. IA therapy cohort: effusions and cysts remained at 2–6 weeks. Synovectomy cohort: regression of effusion and cyst | N | U/A | N | U/A |
| Newman[36] | Y | Y | | | SPP, LR MR | | Effusion presence; Power Doppler signal assessed 1–4 in the SPP | Effusion reduced in all subjects posttherapy. Doppler signal reduced in all knees, at least 2 grades | N | U/A | N | U/A |
| Rubaltelli[40] | Y | Y | | Extension (e) | SPP***, MR, LR | Y | Synovial sac thickness in mm, then graded 0–3 | Significant reduction in ultrasound detected synovitis postsurgery in all sites (SPP, $p < 0.005$, MR, $p = < 0.05$, LR, $p < 0.02$) | Y | Y | N | U/A |
| Salaffi[41] | Y | | | 30° flexion | SPP, LR MR | | Vascularity of SPP calculated through time-intensity curves using Doppler and contrast | 16 of 18 knees had qualitative reduction in Doppler signal changes in ultrasound measurements correlated with changes in clinical measurements | N | U/A | Y | Y |
| Shio[44] | Y | | | | SPP | | Semiquantification of power Doppler signal (0 = 0 signals, 1 = 1–4 signals, 2 = 5–8 signals, 3 > 8 signals). Resistive index (RI) calculated | Significant improvement in the Doppler grade after therapy, but no improvement in RI after therapy | N | U/A | Y | Y |
| van Holsbeeck[48] | Y | | | 30° flexion | SPP | | Maximal synovial thickening in the SPP (anterior and posterior walls) in the AP diameter in mm | Decrease in the synovial thickness at 10 and 14 days. Synovial fluid was present in fewer subjects after therapy | N | U/A | N | U/A |

* Synovium defined as space between femoral cartilage and prefemoral fat pad. ** Synovium defined as matter between femoral cortex and quadriceps tendon. *** Synovium defined as zone between femoral cartilage and prefemoral fat pad. (a) MR and LR defined as regions at the middle third of the patella with the knee extended. (b) MR and LR defined as the vertical plane of the lateral and medial borders of the patella with the biceps femoris contracted and knee extended. (c) MR and LR defined as the regions imaged when the tail of the probe is placed with the tail lying in the middle transaction of the patella. (d) Biceps femoris contracted. (e) Biceps femoris at rest. RA: rheumatoid arthritis; PsA: psoriatic arthritis; OA: osteoarthritis; U/A: unable to assess; SPP: skin perfusion pressure; PD: Power Doppler; PET: positron emission tomography; MRI: magnetic resonance imaging; CRP: C-reactive protein; MMP: matrix metalloprotease; IA: intraarticular; AP: anterior/posterior; U/C: unclear. Y: yes; N: no.

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*Table 4.* Summary of the scintigraphy, including scoring system used, and responsiveness.

| Study | RA | PsA | OA | Label | Scoring System | Description of Response | Statistical Assessment Used to Assess Internal Responsiveness? | Internally Responsive? | Statistical Assessment Used to Assess External Responsiveness? | Externally Responsive? |
|---|---|---|---|---|---|---|---|---|---|---|
| Al-Janabi[9] | Y | | | 99T cm -HMPAO, leukocyte imaging | Unclear | Mean 68% reduction in neutrophil migration post- IA ST | N | U/A | N | U/A |
| Al-Janabi[10] | Y | | | 99T cm- MDP and 99T cm HMPOA labeled white cells | Unclear | Linear correlation between change in neutrophil uptake and change in pain ($R = 0.87$, $p < 0.001$) | N | U/A | Y | Y |
| Beckers[14] | Y | | | 18 F-FDG, PET scan | Standardized value uptakes (SVU). Considered positive when uptake corresponded with site of joint synovium | At 4 weeks, significant correlation between changes in PET, MRI < CRP, MMP-3, but not ultrasound | N | U/A | Y | Y |
| Creamer[16] | | | Y | 99m Tc bone scan | Unclear | 99m Tc demonstrated no difference over time in either group | N | U/A | N | U/A |
| De Bois[19] | Y | | | 99T cm pertechnetate labeled IgG scintigraphy | 0 not increased, 1 = increased faint, 2 = increased moderate, 3 = increased marked | Scintigraphy scores decreased in all knees after therapy | N | U/A | Y | Y |
| Arzu Gencoglu[23] | Y | | | Tc 99m HIG and Tc 99m MDP scans | Quantitative analysis by dividing mean count per pixel in knee by mean count per pixel in adjacent normal bone | Tc 99m HIG index values significantly reduced at 3 months ($p < 0.001$) in the 13 knees that showed clinical response. No significant change in those with a fair or poor clinical response | Y | Y | N | U/A |
| Arzu Gencoglu[24] | Y | | | Tc 99m-labeled polyclonal HIG | Dividing mean pixel count/ pixel region in knee by mean counts/pixel in the adjacent normal bone | No significant change in the imaging results at the knee joint over time | N | U/A | N | U/A |
| Jones[29] | Y | | | 99m Tc HMPAO-labeled neutrophils | Interpolative background subtraction method, expressed as a percentage uptake of dose | Linear reduction in pain decrease and reduction in neutrophil migration<br>5/6 with P32 demonstrated a decrease in swelling and pain | N | U/A | Y | Y |
| Soroa[45] | Y | | | MDP scan | Computer analysis | Data presentation not complete | N | U/A | N | U/A |
| Tennenbaum[46] | Y | | | Tc-99m-MDP and Ga-67 citrate scans | 0–3. Calculated qualitative ratio of joint to bone and joint to soft tissue | Data presentation not complete | N | U/A | N | U/.A |
| Uematsu[47] | | | Y | 99m TC labeled MDP or pyrophosphate | Unclear | 7 had decreased uptake at followup, and 7 had no change | N | U/A | N | U/A |
| Youssef[51] | Y | | | 111 in study and 99m Tc HMPAO study | Time activity curves over the region of interest superimposed on a graph with SE bars, and visually inspected for differences. 2 compartment model based on blood pool activity and uptake into synovium used to derive a curve | Significant decrease in neutrophil ingress in 13/16 knees, occurring within 1.5 hours of therapy.<br>In 2 of the 3 with no decrease, the baseline neutrophil ingress was low | N | U/A | N | U/A |

RA: rheumatoid arthritis; PsA: psoriatic arthritis; OA: osteoarthritis; HMPAO: hexa-methyl-propylene-amine-oxime; IA ST: intraarticular corticosteroid; U/A: unable to assess; MDP: methylene diphosphonate; FDG: fluoro-deoxy-glucose; PET: positron emission tomography; MRI: magnetic resonance imaging; CRP: C-reactive protein; MMP: matrix metalloprotease; HIG: human immunoglobulin.

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