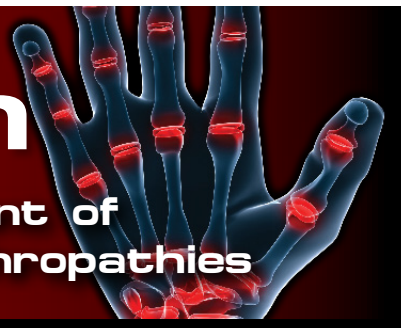
Expert Forum

Imaging and the Practical Management of Rheumatoid Arthritis & Spondyloarthropathies



Making Education Easy

Saturday, 13th April 2013
Waitemata Room, Langham Hotel, Auckland

About the Reviewers

Dr Paul Bird
(FRACP, PhD, Grad Dip MRI)

Dr Bird is a Rheumatologist in private practice and a Senior Lecturer at the University of New South Wales. He is also the Director of Optimus Clinical Research, a clinical research centre undertaking Phase 2, 3 and 4 trials of novel agents for the treatment of rheumatic diseases. Dr Bird is involved in research projects examining the application of magnetic resonance imaging (MRI) in inflammatory arthritis and is an active core member of the OMERACT international MRI imaging. In addition, he is a current member of GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis).

Dr Raoul A Stuart
(BHB, MBChB, FRACP)

Dr Stuart is an Auckland-based rheumatologist in private practice and is a member of the New Zealand Rheumatology Association, British Society of Rheumatology and the American College of Rheumatology. He is currently the President of the New Zealand Rheumatology Association. His interests cover all aspects of rheumatology with large numbers of patients seen with rheumatoid arthritis, psoriatic arthritis and connective tissue diseases. Ultrasound is a routine diagnostic tool in his daily clinical practice.

Sandra Kirby
(CEO, Arthritis New Zealand)

Sandra is passionate about using a research and evidence-based approach in health practice. At Arthritis New Zealand, Sandra's work is spread across a wide range of projects such as prevention, research development and service delivery, as well as ensuring a sustainable ongoing organisation.

Dr Fiona McQueen
(FRACP, MBChB, MD)

Dr McQueen is a consultant rheumatologist at Auckland City Hospital. She has a joint appointment with the University of Auckland, where she is Professor of Rheumatology. She coordinates undergraduate medical rheumatology teaching for the Auckland region and is president-elect of the New Zealand Rheumatology Association. She was a founding member of the OMERACT MRI Imaging group and heads the Auckland Rheumatology Imaging Group. Her research work is specifically related to imaging in inflammatory arthritis, including rheumatoid arthritis, psoriatic arthritis and more recently gout, with a special interest in MRI. She has particular clinical interests in rheumatoid arthritis and the connective tissue diseases.

Dr Anthony Doyle
(BSc, MB, ChB, FRANZCR, ABR)

Dr Doyle runs the Auckland Radiology training programme and he examines for RANZCR. He is also Clinical Associate Professor of Radiology at Middlemore Hospital in Auckland. His principal areas of interest are breast imaging and biopsy, MRI and musculoskeletal radiology. He has published more than two dozen papers in these fields and lectures widely in them.

Welcome

to this review of the Pfizer Speaker Tour on Imaging and the Practical Management of Rheumatoid Arthritis & Spondyloarthropathies, held in Auckland on 13th April 2013. This review summarises the information presented by leading experts, whose presentations discussed a wide range of rheumatic diseases and a wide spectrum of imaging techniques. These techniques are important for their diagnostic and management implications, as well as for providing criteria that determine patient eligibility for use of biologic drugs. Topics included the possible direction rheumatology may take over the next 5–10 years, practical ways of using images in rheumatology, using magnetic resonance imaging (MRI) to assist with decision-making in management of rheumatoid arthritis (RA) and spondyloarthropathy (SpA), and new directions being explored with computed tomography (CT) – single, dual and positron emission tomography (PET).

The day was attended by rheumatologists, radiologists, rheumatology advanced trainees and nurse specialists in rheumatology.

SESSION ONE - IMAGING AND THE PRACTICAL MANAGEMENT OF RHEUMATOID ARTHRITIS & SPONDYLOARTHROPATHIES

Frontiers in Imaging Rheumatology – Dr Paul Bird

Dr Bird's presentation explored four novel imaging concepts in rheumatology:

- Imaging remission and subclinical disease
- Automated image analysis
- Diffusion weighted imaging and osteitis
- Ultrashort Echo Time (UTE) MRI sequence

Subclinical disease – are these invisible entities worth worrying about? Richard Wakefield and colleagues studied 80 patients who underwent a detailed clinical assessment by two physicians who identified the painful joints, which were immediately scanned by a sonographer.[1] Asymptomatic joints were also scanned. The study found:

- Sonography detected more synovitis than clinical examination in patients with oligoarthritis
- In almost two-thirds of patients there was evidence of subclinical disease

These findings were revealed with Grayscale imaging only (no power Doppler or MRI). It might be argued that the substantial amount of synovitis detected in asymptomatic joints and in painful but not swollen joints was explained by the fact that these patients had very active disease – some clinicians might regard these patients as being unlike those in their own practice.

However, more evidence on subclinical inflammation has been published in a study that used methods known to have more sensitivity to synovitis and osteitis – MRI and power Doppler. Brown et al. studied 102 RA patients (median disease duration 7 years) receiving conventional treatment who had been judged by their consultant rheumatologist to be in remission as well as 17 normal control subjects.[2] Conventional 1.5 T MRI, ultrasound and radiographs were conducted at baseline and 12 months. Imaging data were evaluable for 80 patients.

Notably, these patients were the usual mix of patients that are seen in clinical practice. Despite being deemed to be in clinical remission, about half fulfilled American College of Rheumatology (ACR) criteria and half met Disease Activity Score (DAS) criteria. Such evidence demonstrates that when clinical criteria are applied, there is a disconnect between what clinicians think and what is actual disease status. Of the entire study cohort, 96% had evidence of MRI synovitis; a third had moderate-to-severe synovitis and over half had osteitis. In addition, power Doppler investigations revealed synovial hypertrophy in 73% of patients and associated power Doppler flow in ~50%.

The observations so far suggest that the current methods of assessing clinical remission do not necessarily correlate with absence of disease. What is the significance of this subclinical disease?

The OMERACT group assessed databases from 6 cohorts collected from 5 international centres involving RA patients on biologic therapy.[3] A cohort of 213 patients were in clinical remission according to Disease Activity Score28-C-reactive protein (DAS28-CRP <2.6). MRI was assessed according to the OMERACT RA MRI scoring system (RAMRIS). Synovitis was present in the metacarpophalangeal (MCP) joints in 82% of patients and in the wrist in 90% of patients; osteitis was found in 16% and 30%, respectively. In further analyses, the investigators found evidence indicating that a total synovitis score in the hand and wrist of >4 increases the risk of erosive disease.

- A longitudinal analysis of the patients in the Brown et al. study with subclinical disease, whether symptomatic or asymptomatic, showed that they had a reasonable chance of the disease continuing to cause X-ray damage.[2]

Questions currently being investigated include determining the power Doppler threshold in MRI, the number of joints are needed, to work out how best to incorporate imaging into clinical assessment. Not all clinicians have the time or expertise to perform ultrasound, and not everyone can read MRI. Clinicians need to be provided with information that they can incorporate into a patient's record: this is expected to be supplied by automated image analysis, which is intended to provide clinicians with a number they can use.

MRI offers physicians the ability to see minute increment changes in synovitis and erosion over a short period of time, e.g. within a clinical trial lasting only 12 weeks. A reliable, validated scoring system exists that is considered to be the gold standard and is used worldwide in clinical trials (EULAR OMERACT MRI Atlas, OMERACT MRI scoring system).[4-8] However, this system scores in 10% increments and therefore cannot discern very small increments over a short period of time.

A novel 3D automated measurement of MRI synovitis in the MCP and wrist joints of RA patients has proven to be more responsive than the semi-quantitative RAMRIS methods in measurement of erosions, synovitis, joint space width and oedema; this method is also feasible for clinical practice. In a study by Bowes MA et al., the fully automatic quantification of MRI synovitis demonstrated significant changes in volume over 14 months; RAMRIS scoring showed a similar pattern of change but with no significant change at any time point.[9] Modern image analysis methods provide the following advantages for clinicians:

- show greater sensitivity than RAMRIS in validation studies so far
- valuable insight into drug action and interpretation of clinical trial results
- 3D pictures of synovitis show reduction over time and the action is translated into graphs that are quickly and easily read by the clinicians, eliminating the time-intensive task of MRI examinations
- eliminates having to rely on radiologists who might lack the expertise or even interest in MRI interpretation

Using modern image analysis methods as prognostic indicators

Considerable research has focused on scoring of osteitis (formerly termed bone oedema) on MRI scans at the first presentation of RA for predicting future radiographic damage. It is now well recognised that a high osteitis load at baseline equates to a bad prognosis.[10-12] Moreover, biopsies of osteitis areas in RA patients have revealed inflammatory tissue.

However, not all osteitis is associated with a bad prognosis. Investigations are exploring the feasibility of diffusion-weighted MRI for helping to predict bad prognosis osteitis. Diffusion-weighted sequences are being used in addition to normal sequences. T2-weighted images at baseline are associated with a low signal, whereas the diffusion-weighted sequences reveal a high signal, possibly indicative of impaired diffusion and increased risk of erosion.

Ultrashort TE (UTE) imaging is yielding more insights into the structure of bone and may assist in imaging of rheumatic disease. The MR signal from these tissues characteristically decays very rapidly, so they produce little or no signal and appear dark in response to the echo times (TEs) used in conventional clinical imaging. UTE pulse sequences have TEs about 10 to 20 times shorter than the shortest generally available on modern clinical systems. With these sequences, cortical bone can be visualised as the highest signal tissue on an image in spite of its very short T2 of 0.42–0.50 milliseconds. UTE reveals compact bone and spongy (cancellous bone) images and clear definitions of ligaments and tendons, as well as normal periosteum.

Ultrasound imaging in the practical management of RA and spondyloarthropathies – Dr Raoul Stuart

Dr Stuart's presentation focused on practical ways of using images in rheumatology. Ultrasonography has great utility in the clinic; the method can provide multiplanar images of cortical bone, synovium, tendons, muscles, ligaments and nerves, in a short period of time. Clinicians can consider three approaches for acquiring images on ultrasound – rheumatologists will take the "complaint-driven" approach. The other approaches consist of "standardised scanning" and "disease-specific".

Dr Stuart still orders standardised scanning (radiographer and radiologist report); time constraints in the clinic prevent him from performing detailed examinations of some areas (such as the shoulder).

The disease-specific approach is driven by protocol and is less common in rheumatology – e.g. some research has explored the utility of ultrasound in polymyalgia rheumatic disease.

Ultrasound in RA

Ultrasound is useful in the diagnosis of early or late synovitis in RA and has some utility in looking for erosive disease. Dr Stuart acknowledges that we have yet to reach the stage where when we want to treat to target we can readily use ultrasound to determine whether the patient's disease is under control or not. A number of studies have shown that ultrasound is superior to the clinical examination in detecting synovitis. Power Doppler is particularly useful for determining whether the synovitis is definitely active or not.

- High inter-observer agreement has been recorded for ultrasonographic assessment of finger and toe joints in RA patients by 2 investigators with different medical backgrounds – an experienced radiologist and a rheumatologist with limited ultrasound training.[13] Using Grayscale and power Doppler, these investigators showed that synovitis was detected more frequently with ultrasound than with clinical examination. In a comparison of scores, overall agreement was very high: exact agreement was reached in 91% of the examinations with regard to bone erosions, in 86% with regard to synovitis, in 79% with regard to joint effusions, and in 87% with regard to power Doppler signal assessments.

Classification

Szkudlarek described semi-quantitative scales for synovial hypertrophy, effusion Doppler signal and erosions:

Joint effusion was defined as a compressible anechoic intracapsular area (0=no effusion, 1=minimal amount of joint effusion, 2=moderate amount of joint effusion [without distension of the joint capsule], 3=extensive amount of joint effusion [with distension of the joint capsule]).

Synovitis was defined as a noncompressible hypoechoic intracapsular area (synovial thickening) (0=no synovial thickening, 1=minimal synovial thickening [filling the angle between the periarticular bones, without bulging over the line linking tops of the bones], 2=synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the bone diaphysis, 3=synovial thickening bulging over the line linking tops of the periarticular bones and with extension to at least one of the bone diaphyses).

Bone erosions were defined as changes in the bone surface of the area adjacent to the joint (0=regular bone surface, 1=irregularity of the bone surface without formation of a defect seen in 2 planes, 2=formation of a defect in the surface of the bone seen in 2 planes, 3=bone defect creating extensive bone destruction). The ultrasonographer will be looking for an obvious breach of a cortical line. Changes should be evident within both the transverse and longitudinal planes, to be certain of an erosion.

Power Doppler

Power Doppler signal was used to display flow signal in the synovium (0=no flow in the synovium, 1=single vessel signals, 2=confluent vessel signals in less than half of the area of the synovium, 3=vessel signals in more than half of the area of the synovium). Grading increases in terms of strength and intensity.

Power Doppler has proved to be a reliable modality for assessing active MCP joint disease in RA and has been compared with dynamic MRI as a gold standard.[14]

Flow signal on power Doppler ultrasound was detected in 17 of 54 MCP joints examined. Post-contrast MRI revealed a rate of early synovial enhancement (RESE) of ≥1.0%/second in 18 of 54 RA MCP joints. Power Doppler ultrasound showed no flow in 47 of 48 MCP joints with an RESE of <1.0%/second and revealed flow in 16 of 18 MCP joints with an RESE of ≥1.0%/second. Power Doppler ultrasound had high sensitivity (88.8%) and specificity (97.9%).

Investigations have demonstrated correlations between power Doppler sonography and histopathological findings of synovial membrane vascularity.[15] In this study, the knee joints were examined with ultrasound before elective arthroplasty in 23 patients with osteoarthritis or RA. In addition, the vascularity of synovial tissue was evaluated by immunohistochemistry (factor VIII) and was graded qualitatively by a pathologist. There was good correlation between the power Doppler sonography results and the qualitative grading of the vascularity by the pathologist.

Erosion is the hallmark of RA and what we want to prevent. Plain X-rays are still in use but are clearly not as good at detecting erosions as other modalities. Ultrasound can do reasonably well at times. Limitations include the inability to scan all of an MCP joint and some MCP joints scan better than others, e.g. in the hand, the index and the little finger scan better than the middle and the ring fingers.

Clinical examinations using ultrasound compared with other modalities

Wakefield and colleagues were the first to demonstrate that sonography detects more erosion on the MCP joints of rheumatoid arthritis patients than does conventional radiography, especially in early disease.[16]

In 1999, Backhaus et al. compared X-ray, 3-phase bone scintigraphy, ultrasound, and MRI with pre-contrast and dynamic post-contrast examinations in 60 patients with various forms of arthritis including RA, SpA, and arthritis associated with connective tissue disease.[17] Ultrasound and MRI detected more erosions and synovitis compared with X-ray. Scintigraphy detected hot spots, while ultrasound was even more sensitive than MRI in the detection of synovitis.

The same research group conducted a follow-up study two years later and demonstrated that ultrasound remained superior to plain X-ray in the sensitivity to change in bone erosions over time.[18]

Recent study findings have demonstrated the superiority of bilateral ultrasound of MCP and MTP joints and MRI of the dominant hand compared to X-ray in detecting erosive disease in active mild or moderate RA.[19] This cohort of 26 patients (mean age 48 years) had a mean DAS28 score of 3.9 at baseline and a mean disease duration of 19 months. All patients underwent ultrasound and MRI investigations at baseline and at 6 and 12 months. X-rays were taken from hands and forefeet at baseline and after 12 months. MRI was performed at the clinically most active (dominant) hand or forefoot evaluating the MCP 1–5 or MTP 1–5 joints. Ultrasound examination additionally included all other 2nd, 5th MCP and 5th MTP joints. MRI and ultrasound detected erosive disease in 67 and 56 of 78 examinations, respectively ($p<0.01$); X-ray only in 8 of 52 examinations ($p<0.001$). MRI and ultrasound were equally sensitive for detecting synovitis (in 64 and 66 examinations). Synovial power Doppler signals were present in 38 ultrasound examinations. Osteitis was present in 37 MRI examinations. Ultrasound was more sensitive than MRI in detecting tenosynovitis (in 30 vs 15 examinations; $p=0.001$).

Ultrasound utility

The above findings show that both MRI and ultrasound are valuable diagnostic tools, useful in early, mild and moderate disease RA patients. Most clinicians will manage only occasional use of MRIs – whilst ultrasound could be a much more frequently used tool.

A disadvantage of ultrasound includes some blind spots – ultrasound cannot see the entire area of cartilage, e.g. in the shoulder, making ultrasound inferior to MRI in these situations, for detecting erosive change.

Ultrasound use in spondyloarthropathy

Ultrasound has been little studied in SpA; it can be a useful modality in joint synovitis, it has proven utility in examining tenosynovitis and it would be interesting to explore ultrasound in the detection of enthesitis, which is an important part of this disease group.

Examining the enthesis with ultrasound

Such examinations could look for:

- evidence of thickening or enlargement of the tissue, e.g. in the tendon or plantar fascia
- evidence of effusions, spurs (calcific deposits)
- evidence of erosions, new bone formation
- and bursitis may be part of the process.

Power Doppler investigations may reveal an increased signal of vascularity at the site of enthesitis.

Spondyloarthritis: lessons from imaging

Dr Walter Maksymowych reported that ultrasound, particularly using power Doppler, shows promise in the assessment of inflammation, especially the enthesis.[20]

When using ultrasound in patients with SpA, enthesitis will be present in many of them, as illustrated in a study involving 164 patients with SpAs (the majority had ankylosing spondylitis, psoriatic arthritis and reactive arthritis were also present) and 64 controls with other conditions, ultrasound findings consistent with enthesitis were found at ≥1 sites in 161 (98%) SpA patients and the most common sites of involvement were the Achilles tendon and plantar fascia.[21] Of the 1131 sites of enthesitis in the SpA patients, 916 (81%) exhibited vascularisation by power Doppler, always at the site of cortical bone insertion, compared to none of the controls. The study concludes that ultrasound could be useful for both the diagnosis and the assessment of SpA activity, but more research is needed to determine where ultrasound fits.

In Conclusion:

Musculoskeletal ultrasound is a valuable imaging modality for the diagnosis and management of rheumatic diseases. It has bedside utility and is somewhat akin to having a stethoscope. The rheumatologist enhances his/her diagnostic abilities and improves the chances of treating successfully to target. Hopefully, with time, more and more rheumatologists will learn to use ultrasound in their daily clinical practice.

Arthritis NZ – Treatment is more than medicine – Sandra Kirby

Arthritis NZ has used Professor Mason Durie's Whare Tapa Wha model, which summarises wholeness or wellness as needing to involve the four walls of a meeting house, with each wall representing a different dimension and supporting the others: taha wairua – spiritual well-being (the opening of the door); taha whānau – social well-being (the roof); taha tinana – physical well-being (the walls); taha hinengaro – mental and emotional well-being (back wall). Durie's hypothesis is that if only one aspect is treated, then the house is unbalanced.

While the medical system tends to focus on the physical health, Arthritis NZ largely addresses those other aspects of Te Whare Tapa Wha. Its priorities are:

- to undertake public awareness of arthritis
- to work in advocacy, predominantly at systems level advocacy. Improving access to medicines has been advocacy priority – including access to biologics treatment in NZ
- to provide support, information and advice to people affected by arthritis – through website, Arthritis Educator services, support groups of varying kinds, pamphlets and newsletters
- provide funds for research.

Arthritis NZ welcomes the idea of a cohesive nationwide service, whereby patients seeking treatment from Rheumatologists are informed about the services and support offered by Arthritis NZ in the areas of treatment recovery and in their life questions. Most of the people who contact Arthritis New Zealand are surprised, some angry, that their Rheumatologist did not tell them about the services available. Rheumatologists and Clinical Nurse Specialists were encouraged to use the resources and pass this information on to clients.

Sandra's presentation was interlaced with photos from the annual Arthritis New Zealand Children with Arthritis Camp, which this year offered young children (5–12 years) with arthritis a chance to meet, to learn new skills and to build their confidence. This year's camp was supported by Pfizer. A highlight for the children was a visit from rugby league legend Steve Price, who also suffers from arthritis after years of this high-contact sport.

MRI to help solve clinical problems in RA and SpA – Professor Fiona McQueen

Prof. McQueen emphasised the often challenging issues faced by clinicians when making rheumatoid diagnoses. Imaging and, in particular, MRI, has proven very useful in assisting with diagnosis. Difficulties surround the detection of subclinical rheumatoid disease; concomitant fibromyalgia makes diagnosis even more difficult. In these sorts of situations, MRI (and probably also ultrasound) can be very helpful, as illustrated by the case details of a woman who had very little joint-related swelling and completely normal anti-inflammatory markers over an extended period of time. The clinical diagnosis of fibromyalgia was overturned upon MRI examination, which revealed that she met all the criteria for features of erosive inflammatory arthritis. Subsequent treatment for rheumatoid disease improved her condition.

Findings from a study conducted by Prof. McQueen and colleagues are important for demonstrating the positive and negative predictive value of MRI in RA investigations.[22] In a cohort of 42 patients with early RA who underwent MRI scans at baseline, findings that predicted carpal MRI erosions at 1 year included a total MRI score of ≥6 (sensitivity: 93.3%, specificity 81.8%, positive predictive value [PPV] 93.3%; p=0.000007). Conversely, if the total MRI score was low at baseline, X-ray erosions were highly unlikely to develop by 1 year (negative predictive value 0.92). This illustrates a very useful clinical application, in that negative findings on ultrasound and MRI scans can offer reassurance, especially in fibromyalgia cases, for ruling out evidence of inflammatory arthritis.

MRI bone oedema is present in two-thirds of early RA and is a key predictor of both X-ray bone erosion and joint space narrowing, as according to the van der Heijde modified Sharp score after 6 years.[23-28]

Prof. McQueen and colleagues are currently conducting MRI studies into cartilage. Preliminary findings indicate that the baseline MRI bone oedema score was predictive of cartilage score after 3 years. Clinicians need to be aware that cartilage also changes over time in controls with osteoarthritis (OA) – MRI findings may therefore show changes because of concomitant OA rather than rheumatoid processes.

Investigations into the cellular components of MRI bone oedema have helped to clarify the relationship between bone erosion and MRI bone oedema. Twenty-eight bones from 11 patients with RA undergoing orthopaedic surgery subjected to preoperative contrast-enhanced MRI scans were analysed for bone oedema.[29] The samples with MRI bone oedema had a higher density of osteoclasts, macrophages and plasma cells, as well as B cell aggregates, and a trend to increased RANKL expression, compared with samples without MRI bone oedema. Prof. McQueen noted that this is largely why bone oedema is now termed osteitis in RA. However, this sort of pathology has not been proven in psoriatic arthritis or gout. The pathology in OA for bone oedema is different – it appears to involve damage to trabecular bone and fibrous tissue replacing the damaged areas. Prof. McQueen considers therefore that the term bone oedema still applies to those cases with uncertain histology.

Prediction of RA development in early undifferentiated arthritis

MRI has been studied as a tool for early diagnosis of RA in early undifferentiated arthritis (UA).[28] Of 116 patients without a specific rheumatological diagnosis at baseline, 27 had developed RA at the 12-month follow-up; the remainder had self-limiting disease or developed other forms of inflammatory arthritis or osteoarthritis. A prediction model that included as explanatory variables presence of hand arthritis, positivity for rheumatoid factor (RF), early morning stiffness (EMS) lasting >1 hour, and the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI summary score for bone oedema in the MTP and wrist joints correctly identified the outcome of RA or non-RA in 82% of the patients (sensitivity 81%, specificity 82%). These data highlight the need to be cautious of making an RA diagnosis and prescribing treatment too early in early UA patients.

Another study involving 129 patients with UA reports that MRI of the wrists and finger joints in conjunction with serological autoantibodies effectively predicts progression from UA to RA.[30] Patients who were positive for ≥2 of 3 objective measures at baseline – anti-cyclic citrullinated peptide (anti-CCP) antibodies and/or IgM-rheumatoid factor, MRI-proven symmetric synovitis, and MRI-proven bone oedema and/or bone erosion – progressed to RA at 1 year with a 79.7% PPV (75.9% specificity, 68.0% sensitivity). Furthermore, in 22 UA patients positive for both anti-CCP antibodies and MRI-proven bone oedema who were considered to have progressed to RA at 1 year, the PPV was increased to 100%. These findings indicate the utility of MRI (and the finding of bone oedema/osteitis) in patients with UA – especially those who are anti-CCP positive.

MRI pitfalls

Prof. McQueen cautions against relying solely on imaging evidence for diagnoses. Abnormalities can show up in normal controls and mislead clinicians into making false diagnoses. For instance, ulnar-lunate impaction is commonly found in asymptomatic normal controls. The extensive bone oedema within the lunate with cystic change in the ulnar pole and chondral loss could be mistaken for RA.

In addition, normal controls with minimal pain at the thumb base showing MRI evidence of bone oedema could be mistaken for OA change.

Crossover of imaging and clinical problems

A second case illustrates the inherent difficulties with imaging data and clinical presentations. A 69-year-old patient with onset of pain and swelling in large and small joints, widespread active peripheral arthritis and tenosynovitis, was diagnosed with RA (–ve RF, anti-CCP 82U) and started on MTX (20 mg/week), prednisone 20 mg slowly decreasing, diclofenac and intra-articular steroid injections. After 3 months, the response was clinically inadequate; triple therapy was initiated. Three months later, the patient felt fine and presented with 2 swollen, 4 tender joints, and a $DAS28_{CRP}$ 3.7. X-rays showed degenerative change only.

This patient was amongst those recruited for Prof. McQueen's rheumatoid cartilage study, and her MRI scan suggested aggressive disease, showing multiple small erosions, extensive synovitis and bone oedema. Without the MRI scan, the existing treatment regimen (triple therapy) would probably have stayed the same. Escalating to MTX and leflunomide resulted in excellent response but with neutropenia and leukopenia. MRI at 5 years after study entry revealed a reduction in bone oedema, lower $DAS28_{CRP}$, some residual erosions

and synovitis, indicating that very good control can be achieved with standard conventional therapy. If MRI scans could be performed more often in her practice, management might subsequently be changed more frequently.

Progression may still occur in patients who have satisfied remission criteria, suggesting there is ongoing disease activity. MRI has revealed subclinical disease activity in asymptomatic patients with normal joints; MRI showed that 96% had synovitis and 46% had bone oedema.[31] In that same study, ultrasound showed that 73% had synovial hypertrophy and 43% had increased power Doppler signal.

In the GO-BEFORE study, early MRI measures at 12 and 24 weeks independently predicted X-ray changes at 1 and 2 years of follow-up.[32] Specifically, X-ray progression at 1 and 2 years was associated with greater baseline synovitis and bone oedema, as well as less early improvement in both features over the first 24 weeks of follow-up. These data support the use of MRI in clinical trials for early identification of patients with (OR who will develop) structural joint damage progression during follow-up.

MRI in RA Summary

- To diagnose RA
  - Bone oedema especially helpful (but be aware of its presence in asymptomatic normals and in OA cases)
  - "full house" helpful as is "completely normal"
  - But cannot differentiate from PsA, reactive arthritis, etc.
- To monitor response to medications
  - Change in inflammatory markers (osteitis and synovitis)
  - Progression of erosions
  - Can signal need to intensify therapy

Axial Spondyloarthritis – Diagnosis

MRI has many applications in axial SpA and the cases presented by Prof. McQueen illustrate some of the difficulties in this area.

Case: a 20-year-old Caucasian man with a 3-year history of back pain:

- History of lifting injury 2 years ago
- Wakes stiff in the morning
- Takes 30 mins to wear off
- Improves with NSAIDs and movement
- Normal CRP and erythrocyte sedimentation rate (ESR)
- HLAB-27 pos
- X-ray sacroiliac joints normal

Sacroiliac joint MRI can be used to assess inflammatory change. In a German study, consecutive slices of STIR (Short TI Inversion Recovery) sequences of the anterior cartilaginous portion of SI joints showed subchondral bone oedema and resulted in a diagnosis of SpA in a patient whose X-rays would not have supported this diagnosis.[33] Spinal STIR images of the same patient revealed vertebral corner inflammatory lesions and also fat infiltration at anterior corners of the vertebrae.

The new imaging measures have been incorporated into the Assessment of SpondyloArthritis international Society (ASAS) classification criteria, impacting on diagnosis of SpA and RA:

- In patients with ≥3 months of back pain and age of onset <45 years, the criteria allow for sacroiliitis on imaging AND ≥1 SpA feature *OR* HLA-B27 positive AND ≥2 other SpA features.[34]

According to the criteria, active (acute) inflammation on MRI is highly suggestive of sacroiliitis associated with SpA, as well as definite radiographic sacroiliitis according to modified New York criteria. Thus, MRI has assumed an important role, because even if the clinical criteria are suggestive of SpA, it may not be possible to make a diagnosis without the imaging.

However, false positives can complicate diagnosis, as in the following case:

- Sacroiliac MRI - 2 slices showed bone marrow oedema (BME)
  - No sacroiliac joint erosions (CT or X-ray)
  - No spinal lesions
  - Started adalimumab – improved for 1/12
  - Then more pain → etanercept → infliximab . . .
  - (in Aust → golimumab → certolizumab pegol . . .)
- How common are sacroiliac joint BME lesions in normals or in nonspecific back pain?

This question has been addressed by Ulrich Weber and colleagues, who assessed the diagnostic utility of MRI in differentiating patients with SpA from those with nonspecific back pain and healthy volunteers, using a standardised evaluation of MR images of the sacroiliac joints.[35] They stated: "*BME and erosions (of SIJs) were recorded by 2 readers in up to 27% of control subjects with nonspecific back pain and 24% of healthy volunteers without pain*". Prof. McQueen emphasised that although MRI may indicate a clear signal, this does not make the diagnosis: imaging has to be in addition to the clinical history. Moreover, clinicians must ensure that patients undergoing imaging have the right clinical features to make it likely that they have the clinical disease prior to subjecting them to testing and expensive MRI investigations.

Prof. McQueen discussed one other questionable case of SpA – a 30-year-old woman with a 5-year history of back pain suggestive of inflammatory pain but inconsistent response to NSAIDs, accompanied by features typically seen in fibromyalgia; irritable bowel syndrome, migraine. Normal CRP and ESR, HLAB-27 positive, X-ray sacroiliac joints normal.

An MRI of the sacroiliac joints reported indistinct/irregular margins – could be eroded. No bone oedema on T2w images, i.e. no osteitis. A CT scan subsequently showed definite erosions and sclerosis on both sides of the joints, interpreted as sacroiliitis, resulting in a diagnosis of SpA.

Thus, the choice of test is important: clinicians have to look in the right places for the right answers.

MRI in SpA Summary

- To diagnose SpA
  - BME on 2 consecutive slices is incorporated into the ASAS criteria and can indicate pre-erosive SpA
  - May need to use in conjunction with X-ray and CT
    - Better for detailing erosions
  - Potential for false positives
    - implications for management (maybe there is too much emphasis on imaging modalities? These should be used judiciously)

CT – single, dual and PET; new directions – Professor Anthony Doyle

Various issues surround the use of imaging:

- Lack of specificity for the various techniques that are employed is an important issue, as is the concept of Bayesian analysis, which ought to be considered when analysing results of any imaging test.
- Frequently, too little imaging is conducted in normal healthy individuals that would inform clinicians as to what false-positives to expect.
- Reproducibility and standardisation; a baseline scan with one test followed by a repeat scan 6 months later with a different imaging protocol will yield a different result.
- Image proliferation – whereas 20 years ago, the average computed tomography (CT) scan session yielded approximately 50 images, nowadays, dual-energy CT yields 1400 images, while CT/PET (positron emission tomography) yields 3000 images, which must all be analysed.

  Computer-aided assessment might seem to be an ideal tool to deal with image proliferation, but significant challenges remain – the human visual system remains a very effective tool and superior to computer-aided assessments.

CT and PET are photon-driven systems, whereas ultrasound and MRI use radio waves and sound wave energy. CT also uses X-rays, while PET uses gamma rays carried by various different agents, most commonly fluorodeoxyglucose (FDG) and sodium fluoride. Standard X-rays have not changed substantially since its evolution; the average X-ray tube employs a broad spectrum of X-ray energies (i.e., PET, gamma rays, essentially monoenergetic, with a few spikes that represent the characteristic X-rays), all on the spectrum of electromagnetic radiation. New Zealand also has limited access to Australia's synchrotron, a particle accelerator that produces monochromatic beams of X-rays that are like a laser light and yield much better resolution than standard X-rays.

Prof. Doyle considers CT to be the gold standard for establishing erosive disease. A comparative study of multidetector helical CT versus MR scanning in the detection of erosions in the rheumatoid hand established that although most erosions were detected using both modalities, erosion scores were higher on CT than MR scans, especially at the metacarpal bases.[36]

Available techniques for detecting nonerosive disease and arteritis include the CT angiogram, although when studying large parts of the body in younger patients, the use of nonionising techniques such as MR are preferable.

Dual-energy CT (DECT) has a certain amount of specificity. The first performance evaluation of DECT demonstrated the automatic separation of bones and iodine-filled vessels, based mainly on the different atomic weights of the various materials.[37] For example, DECT has proven efficacy for identifying uric acid deposits in joints and periarticular soft tissues in patients suspected of having gout.[38] An advantage of DECT is its ability to generate 3D pictures of tophus volume and even tophi within tendons. However, specificity is an issue: it remains unclear as to what levels of substances are within the tophi to enable their imaging and what critical aspects are involved when adjusting the DECT analysis parameters to most reliably demonstrate tophi and non-tophaceous material.

DECT – caveats

- Reproducibility
- Calibration
- Technical standardisation
- Two energy levels may not be enough

The MARS-CT scanner at the University of Canterbury employs high-resolution multi-energy CT, which is capable of discriminating different energy levels and increases the ability to discriminate between different types of material based on the atomic composition rather than just density. Prof. Doyle predicts that this type of discriminatory ability will be introduced into current therapeutic imaging applications.

Positron Emission Tomography

- ^{18}F unstable isotope made in cyclotron
- Bombard ^{18}O with protons
- Half-life 110 minutes
- Positrons released annihilate with electrons
- Two 511MeV gamma rays emitted at 180°
- Attach to carrier; most commonly FDG or NaF

Fluorine Deoxy-Glucose

- Identifies increased glycolytic activity in cells
- Glucose is preferentially concentrated (increase in membrane glucose GLUT transporters and enzymes, such as hexokinase, responsible for phosphorylation of glucose).
- 2-(fluorine-18)fluoro-2-deoxy-*D*-glucose (FDG) is transported into active cells and phosphorylated to FDG 6-phosphate.
- FDG 6-phosphate is not efficiently metabolised further and accumulates: "metabolic trapping" of FDG is basis for imaging *in vivo* distribution with PET

Molecular imaging by FDG-PET of biological processes enables early identification of disease, differentiate benign from malignant lesions, examines all organs for metastases, and determines therapeutic effectiveness.[39] Notably, FDG-PET enables the imaging of bony metastasis, which is extremely hard to observe on CT scanning.

FDG-PET is more sensitive than any other available method for identifying metastatic disease and also shows up clearly in inflamed tissue, including macrophages, capillaries, and fibroblasts.[40] FDG-PET/CT is capable of showing gross erosive disease. It appears that the sensitivity of FDG-PET is higher than any other method for detecting inflammatory myopathies.[41] Whole-body survey of the overall inflammatory load is an attractive feature, although it does involve a significant radiation dose. Isolating any individual part of FDG-PET is not specific for RA – specificity in typing disease is dependent upon distribution and other features.

NaF pharmacology

- $^{18}F^-$ ions diffuse through EC space
- Exchange with OH of hydroxyapatite on bone surface
- Reflects bone turnover
- Uptake twice that of MDP
- Background uptake very low
- High bone:background ratio

No large verification studies exist, but the hope is that ^{18}F-NaF imaging will enable clinicians to localise which abnormal joints are causing the disease-related symptoms. Preliminary studies in SpA have compared ^{18}F-FDG and ^{18}F-fluoride PET-CT with MRI in AS.[42] Some of the lesions correlated with FDG uptake, while others correlated with NaF uptake. It appears from the work done so far that there are areas of bone proliferation shown on NaF imaging that do not correspond with inflammation seen with FDG-PET and do not correspond with osteitis or enthesitis on MR. More insights are needed to elucidate the meaning of those relationships and how they can contribute to identifying and predicting disease course in AS and similar diseases.

In systemic lupus erythematosus (SLE), ^{18}F-FDG PET depicts lymph nodes extremely well, whereas with standard CT, the lymph node may be normal in size yet contain abnormal cells, or conversely, the node may be enlarged but inactive. In contrast, PET/CT effectively distinguishes between nodes, assesses disease activity and prognosis in SLE patients.[43] PET/CT findings have also demonstrated decreased activity through the anterior brain in neuropsychiatric SLE.

^{18}F-FDG PET visualises large-vessel inflammation in giant-cell arteritis, Takayasu arteritis, and other types of aortitis.[44] In patients with symptoms compatible with polymyalgia rheumatica, findings of increased FDG-uptake in the shoulders, hips, as well as the spinous processes of the cervical and lumbar spine, may suggest this diagnosis. PET clearly has a lot to offer not only in diagnosis, but also in quantification of disease and monitoring therapy.

CT/PET Summary

- FDG: Good sensitivity and relative specificity for inflammation; better for osteolytic lesions, excellent in soft tissues
- NaF: Highest sensitivity and specificity for bone lesions because of uptake and CT (up to 100% in metastatic disease)[45]
- Combined FDG/NaF may be best in some patients
- Highly promising techniques; role in infection, implants, joint disease yet to be determined

Ultrasound elastography of musculoskeletal lesions is under investigation; it has proved to be a challenging modality and is yet to be used routinely in clinical practice.[46]

CT and PET in Rheumatology

- The technology continues to evolve
- DECT has shown promise in gout – more validation is needed
- PET is annihilating matter in a good cause
- Treat the patient, not the images!

OPAL Rheumatology Audit – Dr Paul Bird

Optimising Patient Outcomes in Australian RheumatoLogy (OPAL) is a quality use of medicines initiative that arose out of the realisation that better software was needed to manage an enormous patient population with a lot of data. The outdated software package (Medical Director) being used by group practices was oriented toward general practitioners and proved inadequate for meeting the needs of rheumatology.

Australian rheumatologists teamed up with Software 4 Specialists (S4S) to adopt their *Audit4* clinical software and entered Industry partnership with Roche Australia to provide a customised database across many Australian centres. Roche began with a two-year funding commitment that has subsequently extended to five years and is expected to continue.

Audit4 consists of electronic data capture at the point of consultation (at the time of the consultation or soon afterwards). The programme is ideal for clinicians with high-volume practices, can be used in both the public and private settings, and serves as a database as well as an electronic record. A useful feature of *Audit4* is that it provides a summary of joint scores, function and disease activity, evaluation of remission, and medication record. The software automatically factors in CRP and ESR scores and calculates DAS and Health Assessment Questionnaire (HAQ) scores.

Summary of Features of the S4S *Audit4* Database

- **capable of recording all diagnoses (nonrheumatological and rheumatological)**
- **capable of recording all medications, including biologicals for auditing**
- **generates scripts**
- **incorporates findings from specialist investigations into the record**
- **most results are automatically downloaded; some must be manually entered**
- **can incorporate letters to GPs**
- **tracks and displays DAS and HAQ results in graphs and numbers**
- **set reminders**

Audit4 has become an indispensable part of Dr Bird's practice, both as a useful tool and also to initiate research. Currently, 58 Rheumatologists from private and public practices across Australia contribute data to OPAL, which now contains information on approximately 12,000 patients. This large wealth of data can be used by the OPAL Steering Committee for clinician-driven research, which is subject to strict governance. Roche and S4S set up data-links and clinical projects upon request by clinicians. Specific worksheets are developed for the projects that are fed back to OPAL members on the project who work together, extract and de-identify data for statistical analysis.

Audit4 is an opt-out programme (not an opt-in programme), by which patients are informed that their data will be recorded on a database and may be used (de-identified) for clinical research. Patients are permitted to opt-out of this function; as yet, no patients have opted out.

OPAL data offer tremendous scope for research and support clinicians voicing good ideas. Over the last four years, successful, large-scale projects led by the OPAL Consortium include:

- S4S/OPAL Remission Audit[47]
  - evaluated aggregated data to examine how many RA patients within OPAL clinics were in DAS remission and pharmacological interventions used to achieve remission
- S4S/OPAL SMILE[48]
  - assessed safety of treating RA patients with methotrexate (MTX) alone or in combination with leflunomide, in clinical practice
  - baseline demographic data included comorbidities, hepatitis serology, alcohol use, smoking history, pre-existing lung disease
  - a multicentre, observational, cross-sectional, retrospective safety study, with data de-identified for patient, clinic, and clinician prior to collection from 13 participating rheumatology practices (25 rheumatologists); the study spanned 2–6 years (depending on how long rheumatologists had been using *Audit4*); the only information unable to be obtained was duration of therapy, as not all clinicians had recorded therapy start date
  - 2975 patients were included: 74% female, 26% male, mean age 62 years

- distribution of therapy: MTX monotherapy 52.2%, leflunomide monotherapy 7.3%, MTX plus leflunomide 13.9%, and neither MTX nor leflunomide 26.6%
- comorbid liver disease was reported in 8.1% of patients
- liver function abnormalities were reported in fairly low numbers: 12% of the MTX monotherapy group, 16% of the leflunomide monotherapy group, 19% of the MTX-leflunomide combination group, and 14% of the group not taking either drug. Neutropenia was also relatively rare: in 2.3% of the MTX monotherapy group, 5.5% of the leflunomide monotherapy group, 3.9% of the MTX-leflunomide combination group, and 4.2% of the group not taking either drug. In the majority of cases, neutropenia did not result in cessation of the drug
- 8 patients were identified with pulmonary complications listed as the reason for treatment cessation by the treating physician. To analyse this further, specific ethics approval was obtained and a request for further information was sent to the treating physician. Patient de-identification was maintained using code encryption so that only the treating physician was able to identify the selected patients.
- The subanalysis identified patients with documented lung disease attributed by the treating physician to MTX or leflunomide or the combination. The physicians graded 6 of the patients as having mild disease; 2 were graded as severe.
- MTX was implicated as causal in 4 of the cases; no cases were deemed related to leflunomide. In 3 cases, the adverse event resolved upon cessation of drug treatment, with the remainder unchanged after drug cessation. The majority of cases had pre-existing risk factors (i.e. cigarette smoking, pre-existing interstitial lung disease).
- In conclusion, these real-world data provide reassuring evidence for clinicians using MTX and leflunomide in clinical practice for the treatment of RA – MTX and leflunomide were shown to be well tolerated alone or in combination, and result in few haematological, hepatic, or pulmonary abnormalities.

- S4S/OPAL PREDICT:[49]
  - examined the association between baseline clinical prognostic factors and subsequent DAS remission in 1121 early RA patients (71% female, 29% male)
  - This ongoing longitudinal study has so far amassed 12 months' worth of data
  - Data captured included baseline demographics, mode of disease onset, pattern of joint involvement at onset, smoking status, DAS, RF and CCP titre, time from onset of symptoms to presentation and disease activity at baseline.
  - The strongest baseline predictors of DAS28ESR remission at 12 months were younger age, male and low disease activity at baseline. There was no statistically significant association between joint onset patterns, mode of onset, RF or CCP status and smoking status.
  - The study identifies potential high-risk groups that may benefit from more frequent clinical assessment and therapy adjustment. It is hoped that over the next 5 years of follow-up, the maturing data will provide much more information on clinical parameters that may predict response.
- S4S/OPAL CEDAR:[50]
  - sought to determine choices of biological DMARDs in Australia in routine clinical practice, with the aim of identifying how often patients are switching between DMARDs

    Medication choices in Australia:
    - 3 months of MTX
    - 3 months of leflunomide or another synthetic DMARD
    - 1 of 5 TNFα antagonists (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab)
    - interleukin-6 inhibitor (tocilizumab)
    - chimeric anti-CD20 monoclonal antibody (rituximab)
    - T-cell co-stimulation modulator (abatacept)
    - probably also tofacitinib (as from later in 2013)

    Under Australia's 5-strike rule, subsidised treatment is allowed with 5 biologicals: no patients fail – they respond suboptimally and are switched to another drug.
  - 10,000 patients were included in this study. MTX was the most commonly prescribed DMARD. Etanercept ~12%. The most common reason for stopping medications or prescription substitution = suboptimal response. Escalation of therapy was recorded in ~80% of patients.
  - The study recorded frequent switching between medications and also de-escalation.

The OPAL database yields substantial power in numbers of patients and allows rheumatologists to explore research questions with real-world data. New Zealand's rheumatology community can achieve the same situation.

In Conclusion

The data presented at this meeting showed how rheumatology may make best use of the available imaging techniques in day-to-day practice and yielded valuable insights into what these different techniques might provide in the future.

References

1. Wakefield RJ, et al. Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. Ann Rheum Dis. 2004;63(4):382-5.
2. Brown AK, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. 2008;58(10):2958-67.
3. Gandjbakhch F, et al. Synovitis and osteitis are very frequent in rheumatoid arthritis clinical remission: results from an MRI study of 294 patients in clinical remission or low disease activity state. J Rheum. 2011;38(9):2039-44.
4. McQueen FM, et al. What is the fate of erosions in early rheumatoid arthritis? Tracking individual lesions using x rays and magnetic resonance imaging over the first two years of disease. Ann Rheum Dis. 2001;60(9):859-68.
5. Østergaard M, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005;64 (Suppl 1):i3-7.
6. Bird P, et al. The development of the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005;64 (Suppl 1):i8-10.
7. Conaghan P, et al. The EULAR–OMERACT rheumatoid arthritis MRI reference image atlas: the metacarpophalangeal joints. Ann Rheum Dis. 2005;64 (Suppl 1):i11-21.
8. Ejbjerg B, et al. The EULAR-OMERACT rheumatoid arthritis MRI reference image atlas: the wrist joint. Ann Rheum Dis. 2005;64 (Suppl 1):i23-47.
9. Bowes MA, et al. A novel tool for fully automatic quantification of MRI synovitis in rheumatoid arthritis Is more sensitive to change than the current standard semi-quantitative assessment. Arthritis Rheum. 2010;62 (Suppl 10):118.
10. McQueen FM, 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(7):1814-27.
11. Østergaard M, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. Arthritis Rheum. 2011;63(12):3712-22.
12. Peterfy C, et al. MRI comes of age in RA clinical trials. Ann Rheum Dis. 2013;72(6):794-6.
13. Szkudlarek M, et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. Arthritis Rheum. 2003;48(4):955-62.
14. Szkudlarek M, et al. Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging. Arthritis Rheum. 2001;44(9):2018-23.
15. Walther M, et al. Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. Arthritis Rheum. 2001;44(2):331-8.
16. Wakefield RJ, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000;43(12):2762-70.
17. Backhaus M, 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(6):1232-45.
18. Backhaus M, et al. Prospective two year follow up study comparing novel and conventional imaging procedures in patients with arthritic finger joints. Ann Rheum Dis. 2002;61(10):895-904.
19. Schmidt WA, et al. Low-field MRI versus ultrasound: which is more sensitive in detecting inflammation and bone damage in MCP and MTP joints in mild or moderate rheumatoid arthritis? Clin Exp Rheumatol. 2013;31(1):91-6.
20. Maksymowych WP. Progress in spondylarthritis. Spondyloarthritis: lessons from imaging. Arthritis Res Ther. 2009;11(3):222.
21. D'Agostino MA, et al. Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. Arthritis Rheum. 2003;48(2):523-33.
22. McQueen FM, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. Ann Rheum Dis. 1999;58(3):156-63.
23. McQueen FM, et al. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals a high prevalence of erosions at four months after symptom onset. Ann Rheum Dis. 1998;57(6):350-6.
24. McQueen FM, 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(7):1814-27.
25. Benton N, et al. MRI of the wrist in early rheumatoid arthritis can be used to predict functional outcome at 6 years. Ann Rheum Dis. 2004;63(5):555-61.
26. Haavardsholm EA, et al. Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. Ann Rheum Dis. 2008;67(6):794-800.
27. Hetland ML, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). Ann Rheum Dis. 2009;68(3):384-90.
28. Duer-Jensen A, et al. Bone edema on magnetic resonance imaging is an independent predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. Arthritis Rheum. 2011;63(8):2192-202.
29. Dalbeth N, et al. Cellular characterisation of magnetic resonance imaging bone oedema in rheumatoid arthritis; implications for pathogenesis of erosive disease. Ann Rheum Dis. 2009;68(2):279-82.
30. Tamai M, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. Arthritis Rheum. 2009;61(6):772-8.
31. Brown AK, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum. 2006;54(12):3761-73.
32. Baker JF, et al. Early magnetic resonance imaging measures independently predict 1- and 2-year x-ray progression: results from a large clinical trial. Arthritis Rheum. 2012;64 Suppl 10: 692-3.
33. Pedersen SJ, et al. The diagnostic utility of MRI in spondyloarthritis. Best Pract Res Clin Rheumatol. 2012;26(6):751-66.
34. Rudwaleit M, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.
35. Weber U, et al. The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. Arthritis Rheum. 2010;62(10):3048-58.
36. Perry D, et al. Detection of erosions in the rheumatoid hand; a comparative study of multidetector computerized tomography versus magnetic resonance scanning. J Rheumatol. 2005;32(2):256-67.
37. Flohr TG, et al. First performance evaluation of a dual-source CT (DSCT) system. Eur Radiol. 2006;16(2):256-68.
38. Glazebrook KN, et al. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: initial evaluation. Radiology. 2011;261(2):516-24.
39. Phelps ME. Positron emission tomography provides molecular imaging of biological processes. Proc Natl Acad Sci U S A. 2000;97(16):9226-33.
40. Kubota K, et al. FDG PET for rheumatoid arthritis: basic considerations and whole-body PET/CT. Ann N Y Acad Sci. 2011;1228(1):29-38.
41. Al-Nahhas A, Jawad AS. PET/CT imaging in inflammatory myopathies. Ann N Y Acad Sci. 2011;1228:39-45.
42. van der Laken CJ, et al. Nuclear imaging of rheumatic diseases. Best Pract Res Clin Rheumatol. 2012;26(6):787-804.
43. Curiel R, et al. PET/CT imaging in systemic lupus erythematosus. Ann N Y Acad Sci. 2011;1228(1):71-80.
44. Blockmans D. PET in vasculitis. Ann N Y Acad Sci. 2011;1228(1):64-70.
45. Li Y, et al. Clinical utility of ^{18}F-fluoride PET/CT in benign and malignant bone diseases. Bone. 2012;50(1):128-39.
46. Lalitha P, et al. Musculoskeletal applications of elastography: a pictorial essay of our initial experience. Korean J Radiol. 2011;12(3):365-75.
47. Littlejohn G, et al. Multi-centre, observational study shows high proportion of Australian rheumatoid arthritis patients have inadequate disease control. Arthritis Rheum. 2010;62 Suppl 10:320.
48. Bird P, et al. The SMILE Study -- Safety of Methotrexate in Combination with Leflunomide in Rheumatoid Arthritis. J Rheumatol. 2013;40(3):228-35.
49. Bird P, et al. A longitudinal study of prognostic factors in patients with early RA providing direction for future clinical treatment: Predict study. Arthritis Rheum. 2012;64 Suppl 10:2140.
50. Roberts L, et al. Medication choices and medication survival in a national multicentre community based rheumatoid arthritis cohort. Arthritis Rheum. 2012;64 Suppl 10:387.

Publication of this Expert Forum Review was supported by an educational grant from Pfizer New Zealand Ltd. The content and opinions expressed in this publication do not necessarily reflect the views of Pfizer unless so specified. Treatment decisions based on these data are the full responsibility of the prescribing physician. Before prescribing any of the medicines mentioned in this publication please review the data sheets available at www.medsafe.govt.nz. P7689