The 'disconnect' between synovitis and erosion in rheumatoid arthritis: a result of treatment or intrinsic to the disease process itself?

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The use of advanced imaging modalities has allowed greater understanding of the rheumatoid arthritis (RA) disease process and the links between inflammation and damage. The study by Døhn *et al*[1] reported in this issue of the journal (**see article on page 252.**) is the largest yet published to systematically examine responses to combination anti-tumour necrosis factor (TNF) therapy (adalimumab/methotrexate) in patients naïve to biological agents using MRI, ultrasound (US), plain radiography and high-resolution CT (HRCT) scanning. The inclusion of all four imaging modalities allows important questions to be asked.

First, and most obviously, does anti-TNF therapy/methotrexate prevent the progression of bone erosion? The evidence for this is already very strong from studies using plain radiography to measure outcome,[2] and is supported here at a greater level of detail using MRI and US. An earlier publication from the same study provided the same answer using CT scanning.[3] There was no overall progression in erosion scores (or MRI erosion volumes) over 12 months, but individuals who were progressors or regressors could be identified and progression or regression of an erosion at individual joints over 12 months could also be studied.

The second question relates to whether changes in MRI and/or US measures of inflammation occur in parallel with changes in clinical disease activity and, by implication, whether these modalities could be used to monitor treatment response. In other words, does the detection of imaging synovitis or osteitis (MRI bone oedema) have any added value over detecting and measuring joint inflammation clinically? In this study, improvements in imaging synovitis (MRI and US) and osteitis (MRI) were concordant with reductions in C reactive protein, functional scores and joint counts, as would be expected. This is consistent with the findings of other studies which have also reported both MRI and US to be more sensitive for detecting synovitis than clinical assessment.[1 4] This could also be concluded from findings documented here, as all patients had residual imaging synovitis (MRI and/or US) at 12 months despite responding clinically to anti-TNF therapy. Brown *et al* also reported that imaging synovitis occurred frequently in patients with RA who fulfilled the clinical criteria for remission,[5] suggesting a 'floor effect' for the clinical detection of joint inflammation below which subclinical inflammation can only be revealed by imaging. Concerning the ability of MRI or US to act as tools for monitoring change in synovitis or osteitis, the current study reports only intrareader reliability which was mostly high, as indicated by intraclass correlation coefficients (ICCs) >0.90 for both modalities at most time points. However, there were some important exceptions, including MRI bone oedema scores at baseline and synovitis scores at 12 months, where ICCs were considerably lower than have been reported elsewhere.[6] This needs to be borne in mind when conclusions are drawn regarding the predictive power of these data. Intraobserver reliability for US was uniformly high, and this is consistent with recently published findings by Naredo *et al* who showed power Doppler ultrasound (PDUS) synovitis to be both reproducible and sensitive to change in another large cohort of patients with RA treated with anti-TNF therapy.[4] However, in the current study, interobserver reliability was not tested for either US or MRI, so whether these findings can be generalised to other readers in other settings remains to be seen.

The authors have then asked a third question. Can we predict those individuals or sites within bone where erosion will progress using baseline (pretreatment) imaging data? Interestingly, the clear answer to this question was 'yes', but the parameter that was most informative (and conferred a relative risk (RR) of erosion of 3.3) was not MRI or US synovitis but MRI bone oedema. If bone oedema was 'ever present' versus 'never present', the RR increased to 14.8. In this study, time-integrated scores for synovitis (US and MRI) also predicted erosive progression, but to a much lesser extent. These findings accurately reflect those from an earlier cohort of patients with RA studied at the end of the pre-biologic era and reported in 2003, where bone oedema at first presentation was followed by x-ray erosion at the same site after 6 years with an OR of 6.5.[7] A later and larger study by Hetland *et al* also found that baseline MRI bone oedema (again at the wrist) was by far the strongest predictor of radiographic progression, the association being an order of magnitude greater than with the baseline synovitis score (which was not significant) and eclipsing the influences of anti-CCP positivity and the 28-joint disease activity score.[8] Most recently, Mundwiler *et al* reported similar findings at the feet, confirming both the importance of bone oedema as a prognosticator and the lack of erosive progression overall in patients treated with anti-TNF agents.[9] Only in the study reported by Brown *et al* has MRI bone oedema been found to be less predictive of radiographic erosions than MRI or US synovitis.[10] Interestingly, that group did not use T2-weighted or STIR sequences in their MRI protocol for the detection of bone oedema, as recommended by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system,[11] and this could have influenced the results. Their study did report that PDUS synovitis positively predicted radiographic erosive progression both at the patient and the joint level in patients treated with disease-modifying antirheumatic drugs (DMARDs).[10] The findings from these studies are summarised in table 1.

The outcome measure used to monitor erosion progression in the current study by Døhn *et al* was not the familiar

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Table 1 Studies investigating prediction of progression of joint erosions in patients with rheumatoid arthritis (RA) using baseline imaging parameters

Reference	Year	Study type	Description	Association with erosion progression (radiographic or MRI)		
				MRI bone oedema	MRI synovitis	PDUS synovitis
Døhn [1]	2010	1	52 patients with biologic-naive RA, disease duration 7 years, followed for 12 months on anti-TNF therapy (adalimumab/methotrexate)	Baseline: RR 3.8, p<0.001 Ever: RR 14.8, p<0.0001 AUC score p<0.001	Baseline: RR 0.68, p=0.79 Ever: RR 0.24, p=0.30 AUC score p=0.063	Baseline: RR 7.5, p=0.06 Ever: RR 16.9, p=0.052 AUC score p=0.002
McQueen [6]	2003	1	42 patients with early RA enrolled, disease duration ≤6 months. Full imaging data available for 31. Followed for 6 years on non-biologic DMARDs	Baseline bone oedema score was only MRI feature on multivariate analysis to predict 6-year Sharp score: R^2=0.20, p =0.01. At each bone OR 6.5 (95% CI 2.78 to 18.1) for MRI erosion	Baseline score not predictive of 6-year Sharp score: R^2=0.05, p=0.2. At each bone no association with later erosion, p=0.5	Not included
Hetland [7]	2009	2	130 patients with early RA, disease duration 3.3 years. Combination non-biologic DMARDs including ciclosporin or placebo. Followed for 2 years	Baseline bone oedema score was the only independent predictor of 2-year change in Sharp score (multivariate linear regression) coefficient=0.75 (95% CI 0.55 to 0.94), p=0.001	Baseline synovitis score did not predict change in Sharp score. Coefficient = 0.20 (95% CI −0.09 to 0.48), p=0.17. No AUC analysis	Not included
Mundwiler [8]	2009	1	50 patients with RA recruited; 46 had suitable data, disease duration <5 years. MRI and XR of MTP joints (3–5 bilaterally). Traditional and biologic DMARDs assessed at 12 and 24 months	Baseline bone oedema predicted MRI erosion: OR (6 months = 34.17; 12 months = 68.0). PPV 0.50, NPV 0.99	Synovitis resolved in two-thirds of MTPs when present in isolation. No association with later MRI erosion reported	Not included
Naredo [4]	2008	1	367 patients with RA, complete imaging data in 278. Disease duration 9.6 years. PDUS of 28 joints (shoulders, elbows, wrists, hands, knees). Followed for 12 months	Not included	Not included	Time-integrated values for PDUS signal and RF predicted XR erosion progression, R = 0.64
Brown [10]	2008	1	102 patients with RA in clinical remission treated with DMARDs, complete imaging data in 90. Disease duration 7 years. PDUS and MRI of dominant wrist and MCP joints	Prediction of structural deterioration in the MCP joints (OR 2.26, 95% CI 0.98 to 5.22, p=0.057)	Prediction of structural deterioration in the MCP joints (OR 2.98, 95% CI 1.49 to 5.97, p=0.002)	Prediction of structural deterioration in the MCP joints (OR 12.21, 95% CI 3.34 to 44.73, p<0.001)
Palosaari [9]	2006	1	27 patients with early RA, disease duration ≤12 months, followed up for 1 year and 24 for 2 years with contrast-enhanced MRI	Bone oedema score only baseline variable to predict erosive progression at 2 years on multivariate regression (OR 4.2, 95% CI 1.3 to 13.8). At each bone, predicted erosion at 1 and 2 years: OR 28 (95% CI 11.7 to 67.1) and 14.9 (95% CI 6.3 to 34.9)	Synovitis score (baseline) only predictive of erosion at 2 years on univariate analysis; Spearman correlation coefficient=0.57, p=0.004	Not included

Study type: 1, observational, longitudinal; 2, randomised clinical trial.
AUC, area under the curve; DMARDs, disease-modifying antirheumatic drugs; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal joint; NPV, negative predictive value; PDUS, power Doppler ultrasound; PPV, positive predictive value; RF, rheumatoid factor; RR, relative risk; XR, plain radiography.

Sharp van der Heidje score[12] taken from plain radiographs, but the CT erosion volume measured using Osirix imaging software. This was determined on two occasions and mean volumes at baseline and 1 year were derived to assess progression. In this paper only one observer was used, which was a methodological weakness, albeit a common one repeated in many other studies.[5 8] A more rigorous two-reader approach would be ideal to validate these findings, as has been used in the majority of landmark studies using plain radiographic progression as an outcome.[13] The use of HRCT scanning for detecting RA erosions at the wrist and comparison with MRI scanning was first reported by Perry *et al*.[14] Strong concordance was demonstrated, with 87% of lesions visualised by both modalities. Døhn *et al*[15] performed a similar study at the metacarpophalangeal joints with very similar findings (82% concordance) and, more recently, went on to use HRCT erosion volumes as the primary outcome measure in the companion paper to this one published last year in the journal.[3] Like MRI, HRCT is a tomographic modality and can pick up erosions at complex regions such as the wrist where two-dimensional plain radiography is notoriously unreliable.[16] CT images can clearly reveal the break in the calcified cortical plate indicating the edge of an erosion. This region would be low signal on T1-weighted MRI images and is sometimes poorly visualised—for example, when there is adjacent bony sclerosis.[17] Studies validating HRCT erosions against plain radiographic erosions have been performed[15] and invariably plain radiography comes off a very poor second, especially at sites such as the wrist because of limitations already mentioned, but where radiographic visualisation is better (at the metacarpal heads) all erosions scored on plain x-rays were also scored on CT scans.[15] Reliability was very high for CT erosion volumes in the current study; the data have been presented more fully in the previous companion paper.[3] The use of imaging software to compute CT erosion volumes is an evolving area and also applicable to other erosive arthropathies such as gout where excellent reliability has also been documented.[18]

What then is the 'disconnect'? As referred to in this study, it is the observation that progression of bone erosion can be nil for the cohort overall, despite persistent MRI and US synovitis (observed in 96% and 25%, respectively, at 12 months). This suggests that the anti-TNF/methotrexate combination is affecting bone erosion more than synovitis and that one process is 'disconnected' from the other. This presupposes that they were previously 'connected', with

synovitis being the cause of bone erosion, which should result in both either progressing or remitting together. As alluded to above, this study and several others[1 4 7–9 18] clearly show that osteitis in the subchondral bone (represented by bone oedema on MRI) is far more predictive of the later development of bone erosion (whether detected by MRI or radiographically) than is synovitis. If only synovitis is examined (either by US or MRI), this has been found in some studies to predict erosive progression, especially when cumulative scores over time are examined using an area under the curve analysis.[4] If both bone oedema and synovitis data have been gathered concomitantly and the data subjected to multivariate regression analysis, most studies have concluded that bone oedema is the strongest predictor of erosion,[1 7] apart from the study by Brown *et al* as mentioned above.[5] At this point there are no studies of erosion progression in patients with isolated bone oedema and, indeed, such individuals would be difficult to find as MRI synovitis is such a common finding in RA, occurring in 96% as described here.[1]

Putting this together, it could be hypothesised that there are two pathological processes at work in the rheumatoid joint, one resulting in synovitis and one in osteitis, the latter leading on to erosion as shown by most studies. If these both stemmed from a common precursor pathology which might be centred in the bone marrow, synovitis and osteitis would develop synchronously most of the time and would therefore usually appear together. Thus, it is logical (albeit heretical to many traditionalists) to suggest that synovitis may represent a separate outcome of the inciting disease process and could be regarded as an epiphenomenon. In this scenario, the development and progression of erosions would be most closely associated with osteitis (MRI bone oedema), but there would also be a weaker association with synovitis (as both synovitis and osteitis are sponsored by the same underlying process). This proposal is illustrated in figure 1. The natural history of erosive progression may be modified to a relatively minor degree by traditional DMARDs and steroids or powerfully, as reported here, by anti-TNF therapy.[1]

The idea of 'dual pathology' is not new and harks back to a proposal by Kirwan[20] that a non-synovitis mechanism must contribute to bone erosion. This followed from a study of low-dose steroid in early RA, where groups treated with prednisolone exhibited less radiographic progression than those on other DMARDs despite the same control of clinical synovitis.[20] From another perspective, Molenaar *et al* reported that clinically relevant progression of joint damage does sometimes occur in patients in prolonged clinical remission where there is minimal if any clinical synovitis.[21] Earlier, in 1994, Watson *et al* suggested a 'two-compartment model' for RA with centres of pathology in bone and synovium, supported by immunohistological studies of both tissues.[22] More recently, osteitis within rheumatoid bone has been confirmed at sites where MRI bone oedema was observed prior to surgical resection.[23] Activated osteoclasts adjacent to regions of increased receptor activated nuclear factor κ ligand (RANKL) expression were observed, closely associated with macrophages, plasma cells, T and B cell lymphocytes.[24] The hypothesis built upon this work proposed a bone marrow-centred process underlying RA whereby B lymphocytes play a key role (as suggested by responsiveness to rituximab) and immunocyte activation of osteoclasts via RANKL is the pathway for bone erosion.[25]

Why should anti-TNF therapy have a differential effect on bone and synovium? The most likely explanation centres on interference with osteoclast activity via reduction in levels of RANKL. RANKL-deficient mice, which lack osteoclasts, do not develop bone erosion in an arthritis model induced by serum transfer, while a fusion protein of osteoprotegerin which inhibits RANK–RANKL interactions can prevent bone erosion in TNF-transgenic mice.[26] In humans with RA, the anti-RANKL monoclonal antibody denusomab has recently been shown to reduce progression of MRI erosions without affecting markers of inflammatory disease activity.[27] It is clear that anti-TNF agents also have a profound anti-inflammatory

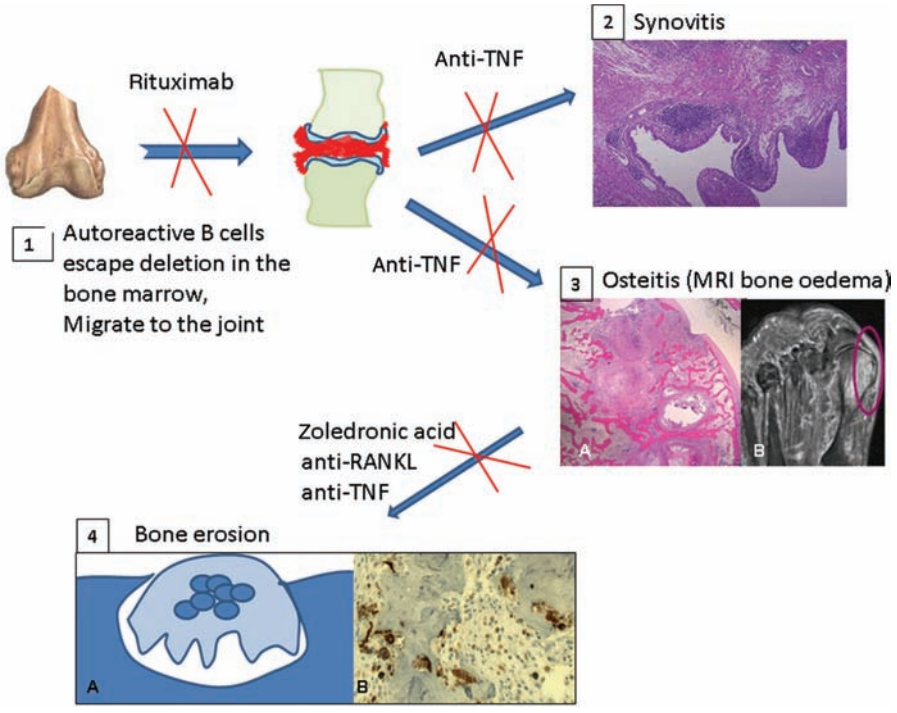

Figure 1 Proposed mechanism for link between inflammation and erosion in rheumatoid arthritis (RA). (1) Autoimmune B cells escape deletion in the bone marrow and traffic to the joint. (2) They migrate to the synovium where they interact with T cells and other inflammatory cells causing synovitis. (3) Cells also traffic to the subchondral bone where osteitis occurs. (4) Bone erosion follows tumour necrosis factor (TNF) and receptor activated nuclear factor κ ligand (RANKL)-mediated activation of osteoclasts. These steps can be blocked as follows: rituximab depletes triggering B cells (interrupts inflammation and erosion), anti-TNF agents block the development of synovitis and osteitis thus blocking erosion and also interfere with RANKL-mediated osteoclast activation. Anti-RANKL agents and zoledronic acid block erosion alone. Image 2 shows inflamed synovium containing lymphocytic aggregates (H&E stain; Ed Klatt MD, WebPath). Image 3A shows the medial eminence of the first metatarsal head resected from a patient with RA revealing an intense inflammatory infiltrate in the subchondral region where a coronal T2-weighted MRI scan shows bone oedema (3B). Image 4A is a diagram of osteoclast eroding bone region of subchondral osteitis showing osteoclasts stained with tartrate-resistant acid phosphatase in resorption pits (4B).

effect resulting in suppression of synovitis and osteitis by inhibition of TNF itself and its downstream cytokine and chemokine cascade.[28] The 'disconnect' referred to by Døhn *et al* and others[1 29] therefore simply reflects the fact that anti-TNF agents have multiple effects and, fortuitously, one of these is on the critical osteoclast-mediated bone destruction pathway. This seems to be particularly sensitive to blockade so, even if osteitis and synovitis still smoulder on in a low-grade manner, anti-TNF agents can shut off the erosive pathway. If desired, this can be targeted separately by anti-RANKL agents such as denusomab or bisphosphonates such as zoledronic acid which inhibit differentiation and function of osteoclasts directly.[30]

In summary, the 'disconnect' is a misnomer. There is no doubt that synovial inflammation, osteitis and bone erosion are all intimately connected. However, much evidence exists to suggest that osteitis is more strongly predictive of bone erosion than synovitis, supporting the notion that there is a more direct connection between bone inflammation and bone damage than between synovial inflammation and bone damage. Synovitis and osteitis might be viewed as cousins with a common ancestor, the process that ultimately drives both remaining obscure but quite possibly sited in the bone marrow. However, the reduction of both synovitis and osteitis is clearly an important therapeutic goal. The detection and monitoring of synovitis is often more feasible in clinical practice using US than MRI scanning, but the latter does afford the opportunity to detect and monitor bone oedema at the same time.

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