After treat-to-target: can a targeted ultrasound initiative improve RA outcomes?

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ABSTRACT

For patients with rheumatoid arthritis (RA), remission can be achieved with tight control of inflammation and early use of disease modifying agents. The importance of remission as an outcome has been recently highlighted by European League Against Rheumatism recommendations. However, remission when defined by clinical remission criteria (disease activity score, simplified disease activity index, etc) does not always equate to the complete absence of inflammation as measured by new sensitive imaging techniques such as ultrasound (US) . There is evidence that imaging synovitis is frequently found in these patients and associated with adverse clinical and functional outcomes. This article reviews the data regarding remission, ultrasound imaging and outcomes in patients with RA to provide the background to a consensus statement from an international collaboration of ultrasonographers and rheumatologists who have recently formed a research network - the Targeted Ultrasound Initiative (TUI) group. The statement proposes that targeting therapy to PD activity provides superior outcomes compared with treating to clinical targets alone and introduces the rationale for a new randomised trial using targeted ultrasound in RA.

The management of rheumatoid arthritis (RA) has changed dramatically over the last few years due to the impact of improved strategies and new therapies. Early diagnosis and effective treatment of RA have been shown to improve symptom control, long-term structural damage and functional status.[1] Rapid escalation of disease modifying antirheumatic drugs (DMARDs) and the early use of biologic agents have been central in increasing the rates of remission by rapidly controlling inflammation.[2–9] European League Against Rheumatism recommendations[10] reinforced by the treat-to-target approach[11] have set remission as the primary treatment goal for RA in everyday clinical practice.

HOW IS CLINICAL REMISSION DEFINED?

For many years, the American College of Rheumatology (ACR) preliminary criteria for clinical remission have been the dominant instrument for measuring remission.[12] These were followed by remission criteria derived from disease activity score (DAS) and DAS28.[13 14] However, both criteria relied on surrogates for inflammation with cut-off values representing remission.

These surrogates have limitations which include the potential underestimation of disease activity in the presence of true joint synovitis[15–22] either due to the insensitivity of clinical assessment or the lack of acute phase elevation. Conversely, such measures may overestimate disease activity (subjective parameters such as tender joint counts (TJC) depend on a patient's pain threshold and coexistent conditions, eg, osteoarthritis and fibromyalgia). Additionally, there is the difficulty of assessing swollen joint counts (SJCs) in established disease because of deformity and residual fibrous tissue, neither of which corresponds to real inflammatory activity. More recent composite criteria, including the simplified disease activity index (SDAI) and clinical disease activity index, still rely on clinical criteria with the above limitations.[23 24] Each is subtly different with respect to its core components, that is, the calculation method used or cut-off level that is applied. The alternative criteria are more stringent than DAS28, but radiographic progression continues in some patients independent of which criteria are used.[22 25 26] Additionally, these criteria were developed for clinical trial purposes and are effective at a 'group level' for evaluating responsiveness and outcomes. However at a 'patient level', due to the previously discussed limitations, clinical remission criteria are unable to accurately define an absence of inflammation and therefore may not represent suitable targets when aiming for tight control. There is general agreement these criteria may, in fact, be defining low disease activity state rather than true remission.

HOW SHOULD REMISSION BE DEFINED AND DETERMINED?

Because of these limitations, the ACR and European League Against Rheumatism, together with OMERACT (Outcome Measures in Rheumatology), have recently worked to redefine remission in RA.[27] Tasked with developing a strict definition of remission at a minimum, including TJC and SJC and an acute phase reactant, this exercise resulted in two definitions of remission, one for clinical trials with C reactive protein and another for clinical practice without:

- when a patient's scores on the following measures are all ≤1: TJC, SJC, C reactive protein and patient global assessment or
- when a patient's score on the SDAI is ≤3.3.

While the standardisation is a major advance, these criteria still depend on the assumption that clinical assessment variables are an accurate reflection of the presence and degree of synovitis and thus can determine signs of synovitis, that is, inflammation.

With increasing evidence that synovitis, the primary site of pathology in RA, is closely linked to the development of radiographic structural damage,[28] it is logical that a definition of remission should relate to the near or complete abolition of synovitis. Therefore, the use of imaging modalities to determine inflammation may be considered necessary to determine future management decisions.

IMAGING AND REMISSION

Imaging techniques such as ultrasound and MRI have the capability to directly visualise both synovitis and bone damage. Both have recently become more readily accessible to clinicians and applied for use in RA. Each has their own advantages and disadvantages, although on a practical level, ultrasound is less expensive, easily repeatable, able to be delivered at the point of care and can be more feasibly used to assess multiple joint areas at one sitting. The relevant MR papers are referenced.[28–34]

Ultrasound can be used to assess two aspects of synovitis: its morphology and quantity using grey scale (GS) and synovial vascularity as measured by colour or power Doppler (PD). It is the latter component that has attracted particular attention as this has been shown to better correlate with inflammatory activity than GS alone.[35]

The aim of this paper is to reflect on recent published data relating to the utility of ultrasound in defining and determining remission in RA patients and to present the outline of a newly planned study attempting to determine the significance of subclinical synovitis. A summary of the key papers relating to ultrasound and remission is given in table 1.

Table 1 Ultrasound and remission: the evidence base

Author	Year	Number of patients	Treatment	Definition of clinical remission for inclusion into study	Joints scanned	Definition of 'imaging remission'	Time to scan
Brown *et al*[15]	2006	107, late DD median 7 years[2–38]	DMARD	As defined by treating rheumatologist	Five joints; dominant wrist and MCPJ2–5	Used a semiquantitative score; did not define imaging remission	30 Min
Wakefield *et al*[36]	2007	10, early DD median 6 m (3–11 months)	Anti-TNF	DAS28 <2.6; NB: patients had active disease at inclusion	42 Joints: shoulders, elbows, wrists, MCPJ, PIPJ, knees, ankles, MTPJ	Semiquantitative score for GS and PD; remission defined as absence of GS and PD	50 Min
Saleem *et al*[16]	2009	100, late DD; median 120 months (72–183)	50 DMARD, 50 anti-TNF	DAS28<2.6	Five joints: dominant wrist and MCPJ2–5	Semiquantitative score for GS and PD; remission defined as absence of GS and PD	30 Min
Balsa *et al*[37]	2010	97, late (mean DD 5.9 years)	DMARD, biologic	As defined by treating rheumatologist	42 Joints: shoulders, elbows, wrists, MCPJ, PIPJ, knees, ankles, TNJ and MTPJ	Semiquantitative for GS and PD; remission defined as an absence of joints with a PD signal	45 Min (including documentation)
Scirè *et al*[38]	2009	106, early	DMARD	DAS<1.6	44 Joints: shoulders, elbows, wrists, MCPJ, PIPJ, SCJ, ACJ, knee, ankle and MTP	Semiquantitative score for PD and GS; did not define imaging remission; calculated a summative score	60 Min
Peluso *et al*[39]	2011	94 (48 early: 6.9 months±3) and 46 late: 118.9 months±71.7)	Early: DMARD±anti %) Late: All DMARD±anti-TNF	DAS<1.6	10 Joints (12 joint areas): bilateral MCPJ 2–3, PIPJ 2–3, wrist (two regions)	**Used 3 definitions: active synovitis** (SH and PD), **US remission:** no SH or PD; **inactive synovitis:** SH but no PD	Not documented
Saleem *et al*[40]	2010	47 (27 early: DD 19 months, 20 late: DD 120 months)	All DMARD and anti-TNF	DAS28<2.6	Five joints: dominant wrist and MCPJ2–5	Semiquantitative score for GS and PD; remission defined as absence of GS and PD	30 Min
Saleem *et al*[48]	2011	128, late; DD 8 years (5–13 years)	DMARD and TNF blocker	DAS28<2.6	Five joints; dominant wrist and MCPJ2–5	Semiquantitative score; imaging remission – 1. no GS or PD; 2. low disease activity (GS≤1) and PD=0; 3. PD=0; 4. PD≤1	30 Min

DAS, disease activity score; DMARD, disease modifying antirheumatic drugs; GS, grey scale; MCPJ, metacarpophalangeal joint; PD, power Doppler; TNF, tumour necrosis factor; US, ultrasound, DD, disease duration; PIPJ, proximal inter-phalangeal joint; TNJ, talo-navicular joint; ACJ, acromio-clavicular joint; MTP, metatarsophalangeal joint; SH, synovial hypertrophy; NB, Nota Bene, note.

HOW DO CLINICAL CRITERIA COMPARE WITH ULTRASOUND CRITERIA?

The first insight into a discrepancy between ultrasound findings and clinical composite indices of remission was from a study by Brown *et al*.[15] The dominant wrists and 2nd–5th metacarpophalangeal joints of 102 patients using conventional DMARDs deemed in clinical remission (as determined by the treating rheumatologists) for least 6 months were scanned using both ultrasound and MRI. It demonstrated that, in at least one scanned joint, 74% and 43% of patients had GS or PD synovitis, respectively. This compared with the very small number of patients who had clinical synovitis. MRI confirmed the ultrasound findings but also highlighted an even higher number of patients with synovitis. More recent studies using ultrasound in different RA groups and scanning different sets of joints have confirmed similar findings.[16 36–39]

In a subsequent study of 128 patients with RA (DAS<2.6; median <1.7) who were taking either DMARD or an antitumour necrosis factor (TNF) agent, ultrasound was performed on the dominant wrist and metacarpophalangeal joint 2–5. In patients fulfilling DAS28, modified ACR or SDAI remission criteria, moderate or severe PD activity was present in 21%, 15% and 19%, respectively. Although more stringent criteria reduced the number of swollen or tender joints, the number of joints with PD did not change.[16]

DOES DISEASE DURATION AFFECT THE CHANCE OF IMAGING REMISSION?

It is accepted that starting treatment early in patients with RA results in higher remission rates, a higher chance of sustained remission after stopping TNFα inhibitors and less radiographic progression when compared with patients who have received delayed treatment.[40–46] Comparisons of imaging assessments in patients with early and late disease have also been published but in non-comparable cohorts.[8 40]

Peluso *et al* aimed to define how many patients in DAS (<1.6) remission reached ultrasound remission in a cohort of patients with early RA (ERA) compared with longstanding RA (LSRA).[8] ERA patients in remission had lower PD scores and were more likely to have absent imaging synovitis (no GS and no PD) (43.7%) when compared with patients with LSRA (17.4%).

Saleem *et al* compared the ultrasound findings in DAS28 remission patients according to the timing of therapy with anti-TNF therapy.[40] Patients who received combination anti-TNF therapy as 'first-line' were compared with patients who received delayed treatment after failing DMARD and fulfilling National Institute for Health and Clinical Excellence criteria. GS synovial hypertrophy was very common in all patients. However, patients from the early treatment group had significantly lower GS synovial hypertrophy scores when compared with patients from the late group (median total score 5 vs 12; p=0.02). Thirty-five percent of patients from the early group and 45% of patients from the delayed treatment group had PD activity (PD>0) (p=0.63). No differences in PD score were noted.

The level of GS synovitis correlates with disease duration, probably reflecting the level of previous inflammation and subsequent fibrotic change.[16] In contrast, the presence of PD is independent of disease duration and therefore appears to be a better marker of inflammation at any given time point.[22]

IS THE ABSENCE OF IMAGING SYNOVITIS IMPORTANT?

Persistent inflammation in RA is known to lead to cartilage and bone destruction[28] and PD is a reflection of inflammation.[35] Thus, it is possible that the key to long-term disease control could be to achieve prompt and substantial control of inflammation measured at the imaging level. The evidence for this will now be discussed.

The impact of PD activity in patients in remission treated with DMARDs has been determined by evaluated studies. Evidence has shown that PD predicts radiographic progression, disease flare and persistence of disease in patients with RA with low disease activity/remission.[38 39 47] In at least one paper, PD activity has been shown to be the best predictor of subsequent joint damage in the affected joint, with an OR of 12. As multivariate analyses were not included, an independent predictive value was not definitively established. Thus, PD can predict radiological progression in certain patients but is it clinically important? One indication of relevance would be a flare of disease, defined as the need to increase therapy. One study found at least 50% patients in remission had a flare within 2 years.[26]

Saleem *et al* recently studied 93 patients deemed in stable DMARDs remission over a 12-month period of whom 26 patients had a flare over the period.[47] Interestingly, the presence of PD was found to be the strongest independent predictor of flare (OR 4.08 (1.26–13.19); p=0.014) as none of the routine clinical indices of remission were predictive. The potential value of PD was also highlighted by Peluso *et al*[39] who noted that only 20% of patients without PD had a flare over 12 months compared with 47.1% who did. Similarly, Scirè *et al* noted that PD was a better predictor of short-term relapse compared with clinical tools (DAS and SJC) with an OR of 12.8.[38]

HOW SHOULD ULTRASOUND SYNOVITIS BE DEFINED?

Though there is strong evidence that clinical measures do not reflect a true absence of synovitis and that ultrasound synovitis is associated with worse clinical and radiographic outcomes in patients, questions remain as to whether aiming for imaging remission is achievable and how it should be defined. There are a number of considerations: for example, which joints should be scanned, which scoring systems should be used (and what cut-offs applied) and likelihood of concurrent OA (osteoarthritis). The studies previously described have involved scanning between 5 and 42 joints; however, for ultrasound to be a feasible imaging modality, with respect to practicality, identifying the minimal number of joints scanned (that still provide the maximum amount of clinically and patient-relevant information) is crucial.

The majority of remission studies have set stringent definitions of remission (ie, absent PD and GS synovial hypertrophy). However, a more feasible definition may include only PD activity; however, the minimal accepted level of PD activity is unknown, but median PD scores of 0.5 based on scanning five hand joints using 0–3 semiquantitative score has been shown to be associated with adverse radiographic and clinical outcomes, respectively.[22]

TARGETED ULTRASOUND IN RA (TURA)

There is now a compelling argument to suggest that the addition of an ultrasound assessment to the management of patients with inflammatory arthritis is likely to improve the prediction of clinical outcomes. Treating to clinical targets, as described, has previously been shown to improve outcome. However, it remains to be determined whether targeting therapy to imaging measures provides superior outcomes compared with treating to clinical targets alone. It is against this background that an international collaboration of ultrasonographers and rheumatologists recently formed an educational and research

network, the targeted ultrasound initiative (TUI) group, in order to undertake an international study in eight countries, the Targeted Ultrasound in RA (TURA) study, that could determine the added value of ultrasound to state-of-the-art management of RA and thus provide a key missing piece of the jigsaw puzzle. This could lead to a paradigm shift in the management of RA and especially if supported by the results of two other ongoing ultrasound based interventional RCTs (Randomised Controlled Trial) in ERA (NCT 00920478 and NCT 01205854).

The TUI group has devised a pragmatic study, (TURA), where patients with RA in sustained clinical remission are randomised to undergo an ultrasound assessment in order to determine the presence of PD. In those patients where an abnormal level of PD is detected, the DMARD treatment will be increased even if the clinical measures demonstrate remission. In those not having an ultrasound, treatment changes will be based on clinical outcome measures alone. It is intended that the study will be an important way forward in understanding the significance of subclinical synovitis especially PD and whether suppression of these will have a significant impact on future structural and functional outcomes. In addition, the minimum clinically important level of ultrasound abnormality will be elucidated.

The aims of this study are: first, if using ultrasound as the target in a study is a feasible approach; second, if by targeting PD, joint inflammation will be reduced and, finally, in patients in whom PD is reduced, if outcomes will be improved compared with clinically similar patients with persistent PD. The secondary aims include determination of the optimal number of joints to be scanned.

The overarching goal of the study is to determine whether the application of ultrasound in clinical practice influences key outcomes. Thus, if positive, the TURA study will provide the evidence to support the routine use of ultrasound in the management RA, a finding that could have major implications for the rheumatology community.

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Notes