Article:
Horton, SC, Tan, AL, Freeston, JE et al. (3 more authors) (2016) Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment to target strategy. Rheumatology, 55 (7). pp. 1177-1187. ISSN 1462-0324

https://doi.org/10.1093/rheumatology/kew037

OXFORD UNIVERSITY PRESS | Rheumatology

Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment to target strategy.

Journal:	*Rheumatology*
Manuscript ID	RHE-15-1154.R1
Manuscript Type:	Original Article (includes systematic reviews)
Date Submitted by the Author:	28-Oct-2015
Complete List of Authors:	Horton, Sarah; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine Tan, Ai Lyn; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine Freeston, Jane; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine Wakefield, Richard; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine Buch, Maya; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine Emery, Paul; Leeds Teaching Hospitals NHS Trust, NIHR Leeds Musculoskeletal Biomedical Research Unit; University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine
Keywords Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:	Rheumatoid arthritis < RHEUMATIC DISEASES, Ultrasonography < DIAGNOSTIC METHODS, DMARDs < THERAPIES, Immunosuppressants < THERAPIES, Immunotherapy < THERAPIES

Discordance between the predictors of clinical and imaging remission in patients with early rheumatoid arthritis in clinical practice: implications for the use of ultrasound within a treatment-to-target strategy.

Sarah C. Horton[1,2], Ai Lyn Tan[1,2], Jane E. Freeston[1,2], Richard J. Wakefield[1,2], Maya H. Buch[1,2]*, Paul Emery[1,2]*.

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, United Kingdom

[2]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

*Maya H Buch and Paul Emery equally contributed to this study

CORRESPONDING AUTHOR: Paul Emery, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds, LS7 4SA. Email: p.emery@leeds.ac.uk

SHORT TITLE: Implications for the use of US in early RA

ABSTRACT

Objective: To assess the prevalence, relationship between and predictors of clinical and imaging remission in early rheumatoid arthritis (RA), achieved with treat-to-target management in clinical practice.

Methods: A prospective observational study was conducted in patients with new-onset RA. The treatment target was remission by disease activity score (DAS28-CRP<2.6). Twelve month outcomes included DAS28-CRP remission, DAS44-CRP remission, ACR/EULAR Boolean remission (BR) and absent or absent/minimal power Doppler activity (PDA) on ultrasound (US) of 26 joints (total PDA score=0 or ≤1, respectively). Logistic regression was conducted to identify baseline predictors of these outcomes.

Results: Of 105 patients with complete 12-month data, the rate of DAS28-CRP remission was 43%, DAS44-CRP remission was 39%, BR was 14%, absent PDA was 40% and

absent/minimal PDA was 57%. Amongst patients achieving clinical remission defined by DAS28-CRP, DAS44-CRP or BR, absence of PDA was observed in 42%, 44% and 40%, respectively; absent/minimal PDA was detected in 62%, 66% and 67%, respectively. On multivariable analysis, shorter symptom duration, male gender, fewer tender joints and lower disability were associated with the clinical remission definitions. Lack of osteoarthritis predicted absence of PDA and lower total baseline PDA predicted absent/minimal PDA.

Conclusion: DAS28-CRP remission and absence of PDA were observed in almost half of patients, but less than a quarter achieved both. Achievement of BR was rare. The low agreement between any of the clinical and imaging outcomes and differences in their predictors highlight the complex interaction between symptoms and synovitis, with implications for treat-to-target management. Long-term follow-up should determine the most appropriate target.

KEY WORDS: Rheumatoid Arthritis, Remission, Ultrasound, Disease Modifying Antirheumatic Drug, Prediction, Early Arthritis Clinic, Treatment to Target.

KEY MESSAGES

Following a treat-to-target approach, 43% of patients with RA achieved DAS28 CRP remission in clinical practice.

In RA patients achieving DAS28-CRP, DAS44-CRP and 2011 ACR/EULAR remission, significant power Doppler activity was observed.

Objective measures of severe RA at baseline were associated with ongoing power Doppler at 12 months.

INTRODUCTION

Trials reveal patients with early rheumatoid arthritis (RA) achieve superior outcomes with treatment to target strategies in comparison to conventional routine care [1-3]. European League Against Rheumatism (EULAR) guidelines recommend this approach [4, 5]. Recommendations include monitoring disease activity using a composite measure at least every 3 months, with optimisation of treatment to achieve a pre-defined target, primarily remission. In 2011, American College of Rheumatology (ACR)/EULAR remission criteria were developed for use in trials [6] and are now recommended as the optimal target for treatment [4]. Two definitions are proposed, based on the simplified disease activity index (SDAI≤3.3) or that developed using a Boolean approach: swollen joint count (SJC), tender

joint count (TJC), C-reactive protein (CRP, mg/dl), and patient global self-assessment (0-10 scale) all ≤1.

Such clinical definitions of remission may be imperfect in delineating patients with true absence of inflammation. Data indicates approximately half of patients achieving SDAI remission and one third of patients achieving Boolean remission (using a 28-joint count), after 12 months of treatment with methotrexate, experience worsening radiographic scores and/or a decrease in physical functioning over the following 12 months[6], highlighting the need for ongoing monitoring. Imaging studies in patients with established RA confirm that despite achievement of a clinical remission state, subclinical synovitis may persist. In patients achieving Boolean remission, power Doppler activity (PDA) was demonstrated in approximately half of patients on ultrasound examination of the dominant hand and wrist[7] and one third of patients within 22 joints (hands, wrists, elbows and knees)[8]. The relevance of PDA in clinical remission and low disease activity states is evident from its relationship with radiographic progression [9, 10] and future disease flare [10-12]. Conversely, studies suggest the clinical remission criteria may be too stringent in a subset of patients, notably those with comorbidities[13].

Ultrasound, by directly assessing the pathology of RA, may enable a more comprehensive approach to defining remission which could guide therapeutic decisions. Imaging remission has been proposed as a goal for therapy[14], supported by a recent study demonstrating a superior rate of disease activity score (DAS44) remission at 18 months in patients receiving treatment targeted to ultrasound remission in comparison to a target of DAS28 low disease activity[15]. Further studies are proposed[16].

Evidence of success of treat-to-target strategies in unselected patients with early RA in clinical practice remains limited[17-20] and data regarding the relationship between clinical and imaging remission in early disease, in particular with respect to the new 2011 ACR/EULAR Boolean criteria, is lacking. Several studies have examined predictors of clinical remission in observational, open-label and randomised studies[19, 21-26]; however, less is understood regarding the predictors of clinical and imaging remission in daily practice which may ultimately facilitate decisions regarding choice of first-line therapy or treatment strategy for individual patients.

We conducted an observational study to assess how the EULAR treat-to-target guidelines, and the paradigm for targeting clinical remission, translate into clinical practice particularly in relation to imaging. The objectives were to evaluate, in early RA, the rates of DAS28 remission, DAS44 remission, 2011 ACR/EULAR Boolean remission and imaging remission, and the agreement between these clinical remission states and imaging remission. An additional aim was to establish predictors of these outcomes.

METHODS

Patients

A prospective observational study was conducted in patients with new-onset inflammatory arthritis (IA) attending the Leeds Early Arthritis Clinic. The study was approved by the Leeds Regional Ethics Committee. All participants provided written consent for inclusion according to the declaration of Helsinki. Patients were managed according to EULAR treat-to-target recommendations when clinically appropriate. The target was remission defined by DAS28 using 4 variables (DAS28-CRP4v<2.6): SJC28, TJC28, CRP and patient visual analogue scale disease assessment (VASDA). This was selected due to its frequent use in clinics, prior to publication of 2011 ACR/EULAR remission criteria, with preference of CRP over erythrocyte sedimentation rate (ESR) due to the dependency of ESR on age and gender[27]. As this definition of remission may allow persistence of swollen joints[28], consultant impression of disease remission also factored in treatment decisions, in accordance with guidelines[5]. Treatment escalation to biologic therapy was as recommended by the National Institute of Clinical Excellence (NICE), i.e. at least high disease activity (DAS28>5.1) after failure of at least two synthetic disease-modifying drugs (DMARDs) including methotrexate.

Criteria for inclusion were enrolment between June 2010 and September 2012, fulfilment of RA criteria (1987 ACR and/or 2010 ACR/EULAR RA classification criteria) and DAS28-CRP4v≥2.6 at baseline (or in the instance of missing patient VASDA, DAS28-CRP3v≥2.6 [DAS28 based on 3 variables: SJC28, TJC28 and CRP]). Exclusions were patients not receiving DMARDs within 3 months of baseline (for example due to contraindications), receiving an alternative non-RA diagnosis within the following 12 months or with missing 12-month outcome data. Inclusion of patients with coexistent osteoarthritis (according to a consultant rheumatologist diagnosis, i.e. consistent symptoms and/or signs) was permitted due to the prevalence of these findings.

Clinical Assessments

Clinical data collection occurred every three months (or as clinically indicated, in accordance with EULAR guidelines[5]). Assessments included examination of 44 joints for swelling and 53 joints for tenderness (including Ritchie Articular Index, RAI) by rheumatologists and rheumatology nurse-specialists.

Adherence to guidelines was assessed by calculating the proportion of patients in whom DAS28-CRP4v was recorded at least every 3 months until achievement of the target

(DAS28-CRP4v<2.6) and DMARD or corticosteroid treatment was escalated at least every 3 months if the target was not met. Escalation in DMARD therapy was defined as addition or switch of synthetic (methotrexate, sulphasalazine, hydroxychloroquine or leflunomide) or biologic DMARD, an increase in dose of DMARD or enrolled in a biologic clinical trial. Corticosteroid treatment escalation included initiation of, or increase in, oral prednisolone, administration of intramuscular, intra-articular or intravenous methylprednisolone, or intramuscular triamcinolone.

Ultrasound

Ultrasound examination of 26 joints (elbows, wrists, second and third metacarpophalangeal [MCP] and proximal interphalangeal [PIP] joints, knees, ankles and metatarsophalangeal [MTP] joints) was performed at baseline and 12 months. Joints were selected on the basis of the frequency of US involvement previously reported in RA[29]. A reduced joint assessment in comparison to the number of joints assessed clinically was conducted in order to optimise feasibility.

Ultrasound was carried out in a routine out-patient setting by a validated sonographer who had undergone training with RJW (experienced EULAR teacher) and who was blinded to the clinical findings. The same machine (GE E9) was used, employing either a 15-8 or 18-8 MHz linear array transducer. Scoring was performed according to a standard operating procedure showing probe positions and scoring scenarios utilising the EULAR/Outcome Measures in Rheumatology Clinical Trials (OMERACT) system. Grey scale synovitis (GS) and PDA at each joint was graded using a previously reported semi-quantitative scale of zero to three[30]. Total GS and PDA scores were calculated for each patient by summation of the respective semi-quantitative scores (0-3) at all 26 joints (maximum total score 78).

Clinical Outcomes

These were DAS28-CRP4v remission (DAS28-CRP4v <2.6) and low disease activity (DAS28-CRP4v<3.2), DAS44-CRP4v remission (DAS44-CRP4v<1.6) and low disease activity (DAS44-CRP4v<2.4) and 2011 ACR/EULAR Boolean remission (SJC44≤1, TJC53≤1, CRP≤10mg/dL and patient VASDA≤10mm).

Imaging Outcomes

Absence of PDA was defined as total PDA score=0. In order to allow for low-level PDA which may be observed, particularly at the wrist and first MTP joints, in healthy individuals[31-35] and/or patients with osteoarthritis[36, 37], the following definitions of

absent/minimal PDA were also considered: total PDA score≤1 (i.e. presence of a maximum of grade 1 PDA in a maximum of any one of the 26 joints) or total PDA score≤1 excluding low-grade PDA (PDA=grade 1) at the wrists and first MTPs (i.e. presence of a maximum of grade 1 PDA in the wrists and/or first MTPs and any one of the following joints: elbow, MCP2-3, PIP2-3, knee, ankle or MTP2-5 joints).

Statistics

Characteristics were described using frequencies for categorical variables and means and standard deviations (SD) for continuous variables following a normal distribution. For non-parametric data, medians and interquartile ranges (IQR) were calculated. To determine any difference between patients included in analyses and those excluded due to missing data, Chi-squared tests (or Fisher's exact tests when appropriate according to the number of expected values) for categorical variables, t-tests for continuous variables following a normal distribution and Mann-Whitney-U tests for non-parametric variables were performed.

Prevalence and bias adjusted kappa statistics were calculated to examine the relationship between the clinical remission endpoints and imaging outcomes. Univariable logistic regression was conducted to investigate factors associated with the clinical remission and imaging outcomes. Multivariable logistic regression analysis was also planned, entering baseline variables demonstrating statistical significance ($p<0.05$) on univariable analysis.

RESULTS

Patients

Two-hundred and seventeen patients were eligible for inclusion in the analysis (Figure 1). No significant difference was observed between baseline DAS28-CRP scores, DAS44-CRP scores or ultrasound parameters in patients included in the analyses (n=105) and those who were lost to follow-up or in whom data was missing (n=112). However, they differed significantly ($p<0.05$) in the following manner: mean age was higher and SJC28, TJC28, SJC44 and RAI were generally lower amongst included patients (Table 1).

Management

The majority of patients commenced DMARDs at baseline (72%) or within the first 4 weeks (15%). Choice of first DMARD was methotrexate in 86%, hydroxychloroquine in 10% and sulphasalazine in 4% of patients. Methotrexate in combination with another DMARD was commenced in the remaining 1%. A contraindication to methotrexate was apparent in 5% of patients, including chronic obstructive airways disease, recent or concurrent infection and

deranged liver function tests. Over 12 months, 9 (9%) and 20 (19%) patients failed treatment with methotrexate or an alternative DMARD, respectively, due to intolerance or an adverse event. Table 2 provides further details of patient management.

The DAS28-CRP4v score was recorded at least every 3 months up to 12 months, or until the target was met, in 76 (72%) patients. Escalation of DMARDs (excluding corticosteroids) was appropriate (i.e. at least every 3 months if DAS28-CRP4v≥2.6) in 53/76 (70%) of these patients. In a further 8 (10%) patients, corticosteroid therapy was escalated at least 3-monthly. Amongst the remaining 15 patients in whom treatment was not escalated despite awareness of DAS28-CRP4v≥2.6, reasons throughout the 12 months were: awaiting effect of previous treatment escalation (n=6), non-inflammatory symptoms only (n=5), acceptable disease control (n=4), contraindication to treatment escalation (n=2), patient declined (n=2), considered for biologic clinical trial (n=2) and isolated flare (n=1).

As the target DAS28-CRP4v<2.6 allows the presence of clinical swelling[28], there is still a role for clinical assessment as recommended within EULAR guidelines. In fact, out of 158 visits at which DAS28-CRP4v<2.6 was observed, DMARD treatment was escalated due to a clinician impression of ongoing inflammatory disease activity at 26 (16%) visits.

Outcomes

At 12 months, rates of DAS28-CRP4v remission (DAS28-CRP4v<2.6) and low disease activity (DAS28-CRP4v<3.2) were 43% and 60%; rates of DAS44-CRP4v remission (DAS44-CRP4v<1.6) and low disease activity (DAS44-CRP4v<2.4) were 39% and 73%. The rate of 2011 ACR/EULAR Boolean remission was 14%. The thirty patients achieving DAS28-CRP4v<2.6 but not meeting the Boolean definition of remission missed the latter due to patient VASDA>10mm (n=23), TJC>1 (n=9), SJC>1 (n=6) and/or CRP>10mg/L (n=6).

In respect to ultrasound, absence of PDA (total PDA score=0) was observed in 42 (40%) patients at 12 months. Absent/minimal PDA, defined by a total PDA≤1, was observed in 60 (57%) patients. If any low-grade PDA (grade 1) at the wrists and/or first MTP joints was also accepted within the definition, seven additional patients achieved minimal PDA; i.e. 64% of patients demonstrated a total PDA score ≤1 excluding PDA=grade 1 at individual wrist and first MTP joints.

Amongst 70 patients attaining DAS28-CRP4v<2.6 at least once over the 12 months, the median (IQR) time to first achievement of DAS28-CRP4v<2.6 was 6 (3-9) months. In patients achieving DAS28-CRP4v remission prior to month 12 (n=61), first DAS28-CRP4v remission was sustained over the remaining follow-up in 27 (44%) patients. The majority of

these patients achieved DAS28-CRP4v remission within the first 6 months; 41% and 70% achieved remission by month 3 and month 6, respectively.

Agreement between Clinical and Imaging Outcomes

Prevalence and bias adjusted kappa statistics illustrate poor agreement between the clinical and imaging outcomes (Table 3). In patients achieving the various definitions of clinical remission at 12 months, absence of PDA (total PDA score=0) was observed in 19/45 (42%) patients achieving DAS28-CRP4v<2.6, 18/41 (44%) patients achieving DAS44-CRP4v<1.6, and 6/15 (40%) patients achieving Boolean remission. Absent/minimal PDA (total PDA score≤1) was observed in 28/45 (62%), 27/41 (66%) and 10/15 (67%) patients, respectively. With exclusion of low-grade PDA (grade 1) at the wrists and/or first MTP joints, absent/minimal PDA was observed in 31/45 (69%) and 29/41 (71%) of patients achieving DAS28-CRP4v and DAS44-CRP4v remission, respectively, whilst rate amongst patients achieving Boolean remission was unchanged.

In patients achieving DAS28-CRP4v<2.6 with ongoing imaging evidence of synovitis (n=26), PDA was observed at the following sites: wrists (n=16), MCP2-3 (n=13), MTP1 (n=4), MTP2-5 (n=4), PIP2-3 (n=4), elbows (n=2) and the knee (n=1). In patients achieving Boolean remission the following joint regions were affected by PDA: MCP2-3 (n=5), wrists (n=4), MTP2-5 (n=1), PIP2-3 (n=1), and elbows (n=1).

In patients lacking any PDA, but with active disease as indicated by DAS28-CRP4v≥2.6 (n=23), median (IQR) values for the DAS28 component variables were TJC28 5(2-9), SJC28 1(0-2), patient VASDA 57(40-57) mm and CRP 9(0-18) mg/dL. Amongst 36 patients lacking any PDA but not achieving Boolean remission, patient VASDA>10mm was the most frequent preclusion to fulfilment of the Boolean criteria (n=32), followed by TJC53>1 (n=24), CRP>10mg/dL (n=15) and SJC44>1 (n=9).

Predictors of Clinical and Imaging Outcomes

Univariable analyses demonstrated achievement of the various clinical remission outcomes was significantly associated with male gender, shorter symptom duration, fewer tender joints and lower HAQ at baseline (Table 4). In comparison, baseline parameters predictive of achievement of imaging outcomes were lack of coexistent osteoarthritis, seronegativity, fewer swollen joints, lower CRP and lower total PDA score on ultrasound. A lower DAS28-CRP3v score at baseline was significantly associated with all outcomes. Excluding PDA=grade 1 at the wrists and/or first MTP joints in the definition of absent/minimal PDA did

not significantly affect the results, therefore only results for total PDA score≤1 amongst all 26 joints are presented.

Results of multivariable analysis, entering baseline variables demonstrating statistical significance ($p<0.05$) on univariable analysis, are shown in Table 5. The composite score (DAS28-CRP) was assessed in univariable analyses, but not in multivariable analysis, because of overlap with its component variables.

DISCUSSION

This large single-centre, contemporary study reveals that at 12 months almost half of patients with new-onset RA achieve the clinical target (DAS28-CRP remission) in daily practice, using EULAR treatment-to-target recommendations as a guide to management. The rate of 2011 ACR/EULAR Boolean remission was significantly lower. In patients achieving a state of clinical remission, regardless of the outcome measure used to define remission (either DAS28, DAS44 or even 2011 ACR/EULAR Boolean remission), any PDA (total PDA score >0) was observed in at least half and significant PDA (total PDA score >1) was apparent in around one third of patients.

The clinical remission rates are consistent with other observational treat-to-target RA cohorts including the multicentre Dutch Rheumatoid Arthritis Monitoring (DREAM) cohort (DAS28 remission and 2011 ACR/EULAR Boolean remission observed in 58%[17] and 21%[38], respectively) and an Italian early arthritis clinic (DAS44 remission in 46%)[19]. Methods of assessment in the DREAM study included 28 joint examination and patient assessment of general health, and it is not clear whether patients' global assessments of disease or more extensive joint examination was available in the assessment of 2011 ACR/EULAR Boolean remission. In the DREAM study, non-adherence to intensifying treatment in appropriate patients was observed in 35% of visits, with the most frequent reasons being a physician impression of clinical remission followed by side-effects[18], which is comparable to our findings.

Importantly, this is the first study to demonstrate the discordance between DAS28 remission, or the more stringent 2011 ACR/EULAR Boolean definition of remission, and imaging remission in early RA. It confirms findings previously reported in smaller studies of patients with early RA achieving DAS44 remission using a DAS44-steered treatment protocol (including methotrexate and TNF-inhibitor therapy): persistence of any PDA was identified in 42% of 48 patients amongst 10 joints (the wrists, second and third MCPs and PIPs)[39], and 41% of 43 patients using a 44-joint ultrasound assessment[12]. Other groups have reported ongoing PDA in patients with established RA across various definitions of clinical remission including DAS28[7, 8, 30, 40, 41], DAS44[10, 39] and 2011 ACR/EULAR Boolean-defined

remission[7, 8], in the hands[7, 30, 39, 42, 43] or amongst more extensive joint assessments[8, 10, 40, 41]. Issues of face validity of the clinical composite measures as indicators of remission, which have previously been raised in established RA, are therefore pertinent to early RA and the current recommended treatment strategy of targeting clinical remission.

A significant proportion of patients with absent or absent/minimal PDA had evidence of clinical disease activity as measured by DAS28-CRP, DAS44-CRP and non-fulfilment of 2011 ACR/EULAR Boolean remission criteria. It is likely, at least for a subset of these patients, that the standardised 26-joint ultrasound assessment missed active joint inflammation in other joints (e.g. hips, shoulders, MCP3-5, PIP3-5). However, reduced ultrasound joint assessments including the elbows, wrists, second and third MCPs, knees, ankles and second to fifth MTPs have previously been shown to correlate well with ultrasound assessment of 44 joints in both patients in clinical remission[40] and those with active disease[44]. Moreover, the likelihood that the presence of tender joints and a high patient global assessment which may be influenced by a complex interaction of factors other than active synovitis (such as chronic pain, side-effects of treatment and the presence of comorbidity) is also relevant, particularly given the characteristics which were evident in these patients.

Baseline predictors of clinical remission outcomes were male gender, shorter symptom duration, fewer tender joints, and lower patient VASDA and HAQ scores. In contrast, lack of osteoarthritis and objective signs of less severe disease (RF and ACPA negativity, fewer clinically swollen joints, and lower CRP and baseline PDA) were associated with favourable imaging outcomes. The latter parameters are arguably more reflective of the primary pathology, active synovitis. Therefore, logically, they should warrant aggressive treatment or treatment escalation if present or if increased above normal levels. These findings, therefore, support current and future research into the use of imaging within the management of early RA.

The strengths of this study are its considerable size for a single-centre study. All assessors were trained, supervised and working within one clinic, limiting variation in prescribing behaviour. Management and data collection conducted in an out-patient clinic setting and the absence of strict inclusion criteria afford a degree of generalisability to daily practice. Of note, the prevalence of comorbidities was significant. Greater than one in ten patients in this real-life cohort displayed a contraindication to commencement of methotrexate or intolerance to it necessitating cessation. In addition, one in twenty patients failed an alternative DMARD to methotrexate.

Despite the planned prospective data collection, a proportion of patients were excluded due to missing data, a significant drawback to this study method. The significantly higher SJC28, TJC28 and RAI of patients with missing follow-up data in comparison to patients included in analyses may be related to the proportion of patients who were subsequently referred to biologics clinical trials or received biologic DMARDs with follow-up in biologics monitoring clinic in which standardised ultrasound does not form part of routine assessments. Loss to follow-up of patients with more severe disease may have falsely elevated the remission rates observed. Limitations in the interpretation of PDA findings must be borne in mind, including its validity in differentiating RA synovitis from findings in healthy joints[31, 32, 35, 41], particularly in the wrist[32, 41], or those attributable to osteoarthritis[35-37]. Nonetheless, prognostic validity of PDA in clinical remission has been demonstrated in relation to the prediction of disease flare[10-12] and radiographic progression[9, 10].

This study provides insights into the translation of treat-to-target within clinical practice. It highlights the difficulties in data collection and adhering to treat-to-target guidelines in a clinical setting and identifies room for improving the outcomes of patients with early RA. A clinically significant proportion of patients achieving DAS28, DAS44 or 2011 ACR/EULAR Boolean remission (now recommended for use as a target for treatment by EULAR) demonstrate PDA on ultrasound. More accurate measurement of inflammatory activity by ultrasound should perhaps be a key determinant in guiding treatment escalation and assessing true absence of disease activity. The differences observed between the disease characteristics at baseline which predicted clinical and imaging remission provide further support for the ongoing investigation into the use of imaging within a treat-to-target strategy; patients with unfavourable subjective factors were less likely to achieve the clinical remission outcomes, whereas factors more directly indicative of inflammatory disease activity predicted persistent active disease on imaging. Failure to achieve absent/minimal PDA was associated with higher PDA at baseline. As persistence of PDA in clinical remission is associated with poor outcomes[9-11] the baseline PDA is a warning. Ultrasound may therefore prove to be a useful tool in discerning an individual's prognosis at diagnosis as well as assessing inflammation on treatment.

ACKNOWLEDGEMENTS

We acknowledge other members of the Leeds Musculoskeletal Biomedical Research Unit for their contribution to data collection, including sonographers Laura Horton and Alwyn Jackson, and Elizabeth Hensor for statistical advice.

DISCLOSURE STATEMENT: The authors have declared no conflicts of interest.

FUNDING: This research was part funded by the National Institute for Health Research (NIHR) through the Leeds Musculoskeletal Biomedical Research Unit and Arthritis Research UK through the Programme Grant "Accurate phenotyping in early arthritis to improve prognosis and prevent evolution to rheumatoid arthritis".

REFERENCES

1 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. The Lancet 2004;364(9430):263-9.
2 Verstappen SMM, Jacobs JWG, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann. Rheum. Dis. 2007;66(11):1443-9.
3 Knevel R, Schoels M, Huizinga TWJ, et al. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann. Rheum. Dis. 2010;69(6):987-94.
4 Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann. Rheum. Dis. 2014;73(3):492-509.
5 Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann. Rheum. Dis. 2010;69(4):631-7.
6 Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63(3):573-86.
7 Saleem B, Brown AK, Keen H, et al. Should imaging be a component of rheumatoid arthritis remission criteria? A comparison between traditional and modified composite remission scores and imaging assessments. Ann. Rheum. Dis. 2011;70(5):792-8.
8 Zufferey P, Möller B, Brulhart L, et al. Persistence of ultrasound synovitis in patients with rheumatoid arthritis fulfilling the DAS28 and/or the new ACR/EULAR RA remission definitions: Results of an observational cohort study. Joint Bone Spine 2014;81(5):426-32.
9 Brown AK, Conaghan PG, Karim Z, 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.
10 Foltz V, Gandjbakhch F, Etchepare F, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum. 2012;64(1):67-76.
11 Saleem B, Brown AK, Quinn M, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann. Rheum. Dis. 2012;71(8):1316-21.
12 Scirè CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology 2009;48(9):1092-7.

13 Thiele K, Huscher D, Bischoff S, et al. Performance of the 2011 ACR/EULAR preliminary remission criteria compared with DAS28 remission in unselected patients with rheumatoid arthritis. Ann. Rheum. Dis. 2013;72(7):1194-9.
14 van der Heijde D. Remission by imaging in rheumatoid arthritis: should this be the ultimate goal? Ann. Rheum. Dis. 2012;71(Suppl 2):i89-i92.
15 Dale J, Stirling A, McInnes IB, Porter D. Targeting ultrasound remission in early rheumatoid arthritis – results of the Taser study (abstract). In: *ACR Annual Scientific Meeting*. San Diego, USA.
16 Wakefield RJ, D'Agostino MA, Naredo E, et al. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Postgrad. Med. J. 2012;88(1042):482-6.
17 Vermeer M, Kuper HH, Hoekstra M, et al. Implementation of a treat-to-target strategy in very early rheumatoid arthritis: Results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort study. Arthritis Rheum. 2011;63(10):2865-72.
18 Vermeer M, Kuper H, Bernelot Moens H, et al. Adherence to a treat-to-target strategy in early rheumatoid arthritis: results of the DREAM remission induction cohort. Arthritis Res. Ther. 2012;14(6):R254.
19 Bosello S, Fedele AL, Peluso G, Gremese E, Tolusso B, Ferraccioli G. Very early rheumatoid arthritis is the major predictor of major outcomes: clinical ACR remission and radiographic non-progression. Ann. Rheum. Dis. 2011;70(7):1292-5.
20 van Hulst LTC, Creemers MCW, Fransen J, et al. How to improve DAS28 use in daily clinical practice?—a pilot study of a nurse-led intervention. Rheumatology 2010;49(4):741-8.
21 Gossec L, Dougados M, Goupille P, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann. Rheum. Dis. 2004;63(6):675-80.
22 Contreras-Yanez I, Rull-Gabayet M, Pascual-Ramos V. Early disease activity suppression and younger age predict excellent outcome of recent-onset rheumatoid arthritis patients treated with conventional disease modifying anti-rheumatic drugs. Clin. Exp. Rheumatol. 2012;30(3):402-8.
23 Möttönen T, Hannonen P, Korpela M, et al. Delay to institution of therapy and induction of remission using single-drug or combination–disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. Arthritis Rheum. 2002;46(4):894-8.
24 Ma MHY, Ibrahim F, Walker D, et al. Remission in Early Rheumatoid Arthritis: Predicting Treatment Response. J. Rheumatol. 2012;39(3):470-5.
25 Gremese E, Salaffi F, Bosello SL, et al. Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. Ann. Rheum. Dis. 2012.
26 Wevers-de Boer K, Visser K, Heimans L, et al. Remission induction therapy with methotrexate and prednisone in patients with early rheumatoid and undifferentiated arthritis (the IMPROVED study). Ann. Rheum. Dis. 2012;71(9):1472-7.
27 Crowson CS, Rahman MU, Matteson EL. Which Measure of Inflammation to Use? A Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein Measurements from Randomized Clinical Trials of Golimumab in Rheumatoid Arthritis. J. Rheumatol. 2009;36(8):1606-10.
28 Mäkinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? Ann. Rheum. Dis. 2005;64(10):1410-3.
29 Naredo E, Gamero F, Bonilla G, Uson J, Carmona L, Laffon A. Ultrasonographic assessment of inflammatory activity in rheumatoid arthritis: comparison of extended versus reduced joint evaluation. Clin. Exp. Rheumatol. 2005;23(6):881-4.
30 Brown AK, Quinn MA, Karim Z, 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.
31 Millot F, Clavel G, Etchepare F, et al. Musculoskeletal ultrasonography in healthy subjects and ultrasound criteria for early arthritis (the ESPOIR cohort). J. Rheumatol. 2011;38(4):613-20.

32 Terslev L, Torp-Pedersen S, Qvistgaard E, von der Recke P, Bliddal H. Doppler ultrasound findings in healthy wrists and finger joints. Ann. Rheum. Dis. 2004;63(6):644-8.
33 Carotti M, Salaffi F, Morbiducci J, et al. Colour Doppler ultrasonography evaluation of vascularization in the wrist and finger joints in rheumatoid arthritis patients and healthy subjects. Eur. J. Radiol. 2012;81(8):1834-8.
34 Kitchen J, Kane D. Greyscale and power Doppler ultrasonographic evaluation of normal synovial joints: correlation with pro- and anti-inflammatory cytokines and angiogenic factors. Rheumatology 2015;54(3):458-62.
35 Hameed B, Pilcher J, Heron C, Kiely PDW. The relation between composite ultrasound measures and the DAS28 score, its components and acute phase markers in adult RA. Rheumatology 2008;47(4):476-80.
36 Mathiessen A, Slatkowsky-Christensen B, Kvien TK, Hammer HB, Haugen IK. Ultrasound-detected inflammation predicts radiographic progression in hand osteoarthritis after 5 years. Ann. Rheum. Dis. 2015. http://ard.bmj.com/content/early/2015/04/01/annrheumdis-2015-207241.abstract Accessed April 1 2015.
37 Keen HI, Wakefield RJ, Grainger AJ, Hensor EMA, Emery P, Conaghan PG. An ultrasonographic study of osteoarthritis of the hand: Synovitis and its relationship to structural pathology and symptoms. Arthritis Care Res. 2008;59(12):1756-63.
38 Vermeer M, Kuper HH, Moens HJB, et al. Sustained Beneficial Effects of a Protocolized Treat-to-Target Strategy in Very Early Rheumatoid Arthritis: Three-Year Results of the Dutch Rheumatoid Arthritis Monitoring Remission Induction Cohort. Arthritis Care Res. 2013;65(8):1219-26.
39 Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann. Rheum. Dis. 2011;70(1):172-5.
40 Naredo E, Valor L, De la Torre I, et al. Ultrasound Joint Inflammation in Rheumatoid Arthritis in Clinical Remission: How Many and Which Joints Should Be Assessed? Arthritis Care Res. 2013;65(4):512-7.
41 Balsa A, de Miguel E, Castillo C, Peiteado D, Martín-Mola E. Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard. Rheumatology 2010;49(4):683-90.
42 Gärtner M, Mandl P, Radner H, et al. Sonographic Joint Assessment in Rheumatoid Arthritis: Associations With Clinical Joint Assessment During a State of Remission. Arthritis Rheum. 2013;65(8):2005-14.
43 Salih Ozgocmen MD, Huseyin Ozdemir MD, Adem Kiris MD, Zulkif Bozgeyik MD, Ozge Ardicoglu MD. Clinical Evaluation and Power Doppler Sonography in Rheumatoid Arthritis: Evidence for Ongoing Synovial Inflammation in Clinical Remission. South. Med. J. 2008;101(3):240-5.
44 Naredo E, Rodríguez M, Campos C, et al. Validity, reproducibility, and responsiveness of a twelve-joint simplified power doppler ultrasonographic assessment of joint inflammation in rheumatoid arthritis. Arthritis Care Res. 2008;59(4):515-22.
45 Koski JM, Saarakkala S, Helle M, et al. Assessing the intra- and inter-reader reliability of dynamic ultrasound images in power Doppler ultrasonography. Ann. Rheum. Dis. 2006;65(12):1658-60.
46 Wakefield RJ, Brown AK, O'Connor PJ, Emery P. Power doppler sonography: Improving disease activity assessment in inflammatory musculoskeletal disease. Arthritis Rheum. 2003;48(2):285-8.
47 Joshua F, De Carle R, Rayment M, et al. Power Doppler 'blanching' after the application of transducer pressure. Australas. Radiol. 2005;49(3):218-21.
48 Torp-Pedersen ST, Terslev L. Settings and artefacts relevant in colour/power Doppler ultrasound in rheumatology. Ann. Rheum. Dis. 2008;67(2):143-9.
49 Ellegaard K, Torp-Pedersen S, Henriksen M, Lund H, Danneskiold-Samsøe B, Bliddal H. Influence of recent exercise and skin temperature on ultrasound Doppler

measurements in patients with rheumatoid arthritis—an intervention study. Rheumatology 2009;48(12):1520-3.
50 Strunk J, Strube K, Klingenberger P, Müller-Ladner U, Lange U. Two- and three-dimensional Doppler sonographic evaluation of the effect of local cryotherapy on synovial perfusion in wrist arthritis. Rheumatology 2006;45(5):637-40.
51 Lee V, Zayat A, Wakefield RJ. The effect of joint position on Doppler flow in finger synovitis. Ann. Rheum. Dis. 2009;68(4):603-4.
52 Zayat AS, Freeston JE, Conaghan PG, Hensor EMA, Emery P, Wakefield RJ. Does joint position affect US findings in inflammatory arthritis? Rheumatology 2012;51(5):921-5.
53 Bruyn GAW, Naredo E, Möller I, et al. Reliability of ultrasonography in detecting shoulder disease in patients with rheumatoid arthritis. Ann. Rheum. Dis. 2009;68(3):357-61.
54 D'Agostino MA, Wakefield R, Filippucci E, et al. Intra- and inter-observer reliability of ultrasonography for detecting and scoring synovitis in rheumatoid arthritis: a report of a EULAR ECSISIT task force (abstract). Ann. Rheum. Dis. 2005;64(Suppl III):62.

Figure 1: Patient disposition.

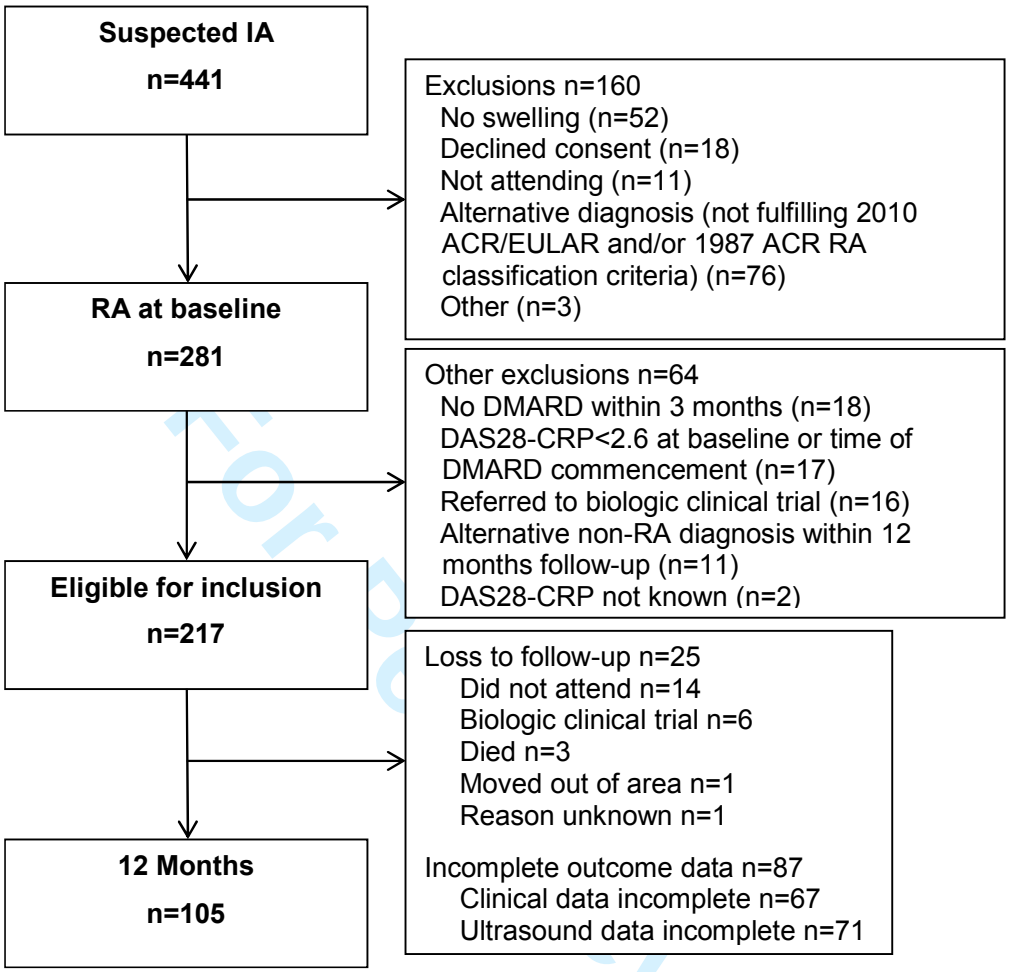

Table 1: Baseline characteristics

	Included in analysis		Excluded due to missing follow-up data		p
	(n=105)	Missing Values	(n=112)	Missing Values	
Age, mean (SD), years	59 (13)	-	53 (15)	-	**0.002**
Female, N (%)	79 (75)	-	80 (71)	-	0.5
BMI, mean (SD)	27 (5)	13	29 (6)	12	0.1
Symptom duration, median (IQR), months	6 (4-13)	-	7 (4-13)	-	0.5
Current/previous smoker, N (%)	65 (62%)	-	67 (60%)	1	0.8
Number of comorbidities[a], N (%)					
1	34 (32%)	-	25 (22%)	-	0.9
2	19 (18%)		31 (28%)		
3	15 (14%)		14 (13%)		
≥4	7 (7%)		7 (6%)		
History/current evidence of coexistent osteoarthritis[b], N (%)	46 (44%)	-	37 (33%)	-	0.1
RF positive, N (%)	78 (74%)	-	72 (64%)	-	0.1
ACPA positive, N (%)	81 (77%)	-	73 (65%)	-	0.05
Fulfilment of RA classification criteria, N (%)					
1987 ACR RA	73 (70%)	-	83 (74%)	-	0.5
2010 ACR/EULAR RA	101 (96%)	-	109 (97%)	-	0.7
TJC28, median (IQR)	7 (3-13)	-	10 (5-17)	-	**0.003**
SJC28, median (IQR)	4 (2-8)	-	6 (3-10)	-	**0.03**
RAI, median (IQR)	7 (4-10)	17	9 (5-13)	24	**0.01**
SJC44, median (IQR)	5 (3-9)	17	7 (4-13)	24	**0.01**
CRP, median (IQR), mg/L	21 (7-45)	-	13 (0-40)	-	0.2
Patient VASDA, median (IQR), mm	50 (31-77)	27	61 (35-82)	44	0.3
DAS28-CRP3v, median (IQR)	4.5(3.8-5.2)	-	4.7(3.7-5.8)	-	0.1
DAS28-CRP4v, median (IQR)	4.9(4.0-5.5)	27	5.1(3.9-6.1)	44	0.5
DAS44-CRP4v, median (IQR)	3.1(2.6-3.6)	34	3.4(2.6-4.0)	46	0.1
HAQ, median (IQR)	1.3(0.8-1.9)	30	1.4(0.5-1.8)	40	0.9
Ultrasound of 26 joints:					
Total GS score[c]	17 (10-25)	21	19 (12-26)	33	0.2
Total PDA score[c]	3 (0-8)	21	3 (0-9)	33	0.9
Absence of PDA (total PDA[c]=0)	23 (27%)	21	55 (28%)	33	0.9
Absent/minimal PDA (total PDA[c]≤1)	34 (40%)	21	61 (35%)	33	0.5
Radiographic erosion in the hands and feet, N (%)					
Any	18 (17%)	-	20 (18%)	2	0.8
1987 ACR definition	11 (10%)		16 (14%)	2	0.4
2010 ACR/EULAR definition	9 (9%)		9 (8%)	2	0.9

[a]Hypertension, hypercholesterolaemia, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, asthma, chronic obstructive airways disease, diabetes, peptic ulcer disease, chronic kidney disease, chronic liver disease, epilepsy, demyelination, depression, thyroid dysfunction, cancer. [b]Osteoarthritis was defined according to a consultant rheumatologist diagnosis (i.e. symptoms and signs consistent with osteoarthritis). [c]Sum of GS or PDA semi-quantitative score assessed in 26 joints (GS or PDA graded between 0 and 3 for each joint, maximum total score 78). Bold text indicates statistical significance at the level of p<0.05. SD: standard deviation, BMI: body mass index, SJC: swollen joint count, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated protein antibody, ACR: American College of Rheumatology, EULAR: European League Against Rheumatism, RA: rheumatoid arthritis, TJC: tender joint count, RAI: Ritchie Articular Index, CRP: C-reactive protein, VASDA: visual analogue scale global disease assessment, DAS28-CRP3v: disease activity score using 3 variables (SJC28, TJC28 and CRP), DAS28-CRP4v: disease activity score using 4 variables (SJC28, TJC28, CRP and patient VAS global disease assessment), DAS44-CRP3v: disease activity score using 3 variables (SJC44, RAI and CRP), DAS44-CRP4v: disease activity score using 4 variables (SJC44, RAI, CRP and patient

VAS global disease assessment), HAQ: Health Assessment Questionnaire, GS: grey scale synovitis, PDA: power Doppler activity; N: number.

Table 2: Management over 12 months

	Early RA n=105
Ongoing Treatment at 12 months, N (%)	
MTX monotherapy	38 (36%)
SSZ monotherapy	3 (3%)
HCQ monotherapy	5 (5%)
MTX + other DMARD	36 (34%)
2 DMARDs (excluding MTX)	1 (1%)
MTX + SSZ + HCQ	8 (8%)
Biologic therapy	5 (5%)
Referred to Biologics Clinical Trial	2 (2%)
Other DMARD	2 (2%)
Steroid alone	4 (4%)
None	1 (1%)
Ongoing MTX use at 12 months	
Administered orally, N (%)	75 (76%)
Administered subcutaneously, N (%)	14 (13%)
Weekly dose, median (IQR), mg	25 (20-25)
Receiving significant total steroid dose over 12 months, N (%)	
≥80mg triamcinolone	10 (10%)
≥150mg prednisolone	30 (29%)
≥120mg methylprednisolone	84 (80%)
Total methylprednisolone dose over 12 months, median (IQR), mg	240 (120-360)
Adherence to treatment to target guidelines, N (%)	
Clinical assessment at least every 3 months until the target for treatment (DAS28-CRP4v <2.6) was met	97 (92%)
DAS28-CRP4v available at least every 3 months until the target for treatment (DAS28-CRP4v <2.6) was met	76 (72%)
DAS28-CRP4v available at least every 3 months and DMARD therapy escalated if the target was not met	53 (51%)
DAS28-CRP4v available at least every 3 months and DMARD or corticosteroid therapy escalated if the target was not met	61 (58%)

MTX: methotrexate, SSZ: sulphasalazine, HCQ: hydroxychloroquine, DMARD: disease-modifying anti-rheumatic drug, DAS28-CRP4v: disease activity score using 4 variables (SJC28, TJC28, CRP and patient VAS global disease assessment).

Table 3: Agreement between clinical remission and imaging outcomes at 12 months (n=105)

Clinical Outcomes	Absence of PDA activity in 26 joints (total PDA score[b]=0)					Absent/minimal PDA activity in 26 joints (total PDA score[b]≤1)					Absent/minimal PDA activity in 26 joints (total PDA score[b]≤1, excluding PDA=grade 1 in the wrists and/or first MTPs)				
	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK	Clinical and imaging outcome	Clinical outcome only	Imaging outcome only	Neither clinical nor imaging outcome	PABAK
DAS28-CRP4v remission (DAS28-CRP4v<2.6)	19 (18%)	26 (25%)	23 (22%)	37 (35%)	0.07	28 (27%)	17 (16%)	32 (30%)	28 (27%)	0.07	31 (30%)	14 (13%)	36 (34%)	24 (23%)	0.05
DAS44-CRP4v remission (DAS44-CRP4v<1.6)	18 (17%)	23 (22%)	24 (23%)	40 (38%)	0.10	27 (26%)	14 (13%)	33 (31%)	31 (30%)	0.10	29 (28%)	12 (11%)	38 (36%)	26 (25%)	0.05
Boolean remission[a]	6 (6%)	9 (9%)	36 (34%)	54 (51%)	0.14	10 (10%)	5 (5%)	50 (48%)	40 (38%)	-0.05	10 (10%)	5 (5%)	57 (54%)	33 (31%)	-0.18

Values are number of patients (percentage of patients), unless otherwise stated. [a]2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA≤10mm). [b]Sum of PDA semi-quantitative score assessed in 26 joints (PDA graded between 0 and 3 for each joint, maximum total score 78). PDA: power Doppler activity, PABAK: prevalence and bias adjusted kappa, DAS28-CRP4v: disease activity score using 4 variables (SJC28, TJC28, CRP and patient VASDA), DAS44-CRP4v: disease activity score using 4 variables (SJC44, RAI, CRP and patient VASDA).

Table 4: Univariable analyses: baseline variables predictive of achievement of clinical and imaging outcomes at 12 months

	DAS28-CRP4v<2.6		DAS44-CRP4v<1.6		Boolean Remission[a]		Total PDA score[b]=0		Total PDA score[b]≤1	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age	1.01(0.98-1.04)	NS	1.01(0.98-1.04)	NS	1.01(0.96-1.05)	NS	0.98(0.95-1.01)	NS	0.98(0.95-1.01)	NS
Female	0.45(0.18-1.11)	NS	**0.36(0.15-0.89)**	**0.03**	**0.31(0.10-0.95)**	**0.04**	0.58(0.24-1.42)	NS	0.63(0.25-1.59)	NS
BMI	0.94(0.87-1.02)[e]	NS	0.96(0.88-1.04)[e]	NS	0.94(0.82-1.07)[e]	NS	1.01(0.93-1.09)[e]	NS	1.00(0.93-1.09)[e]	NS
Symptom duration, months	**0.92(0.86-0.99)**	**0.03**	**0.93(0.87-1.00)**	**0.05**	1.00(0.92-1.08)	NS	0.99(0.94-1.05)	NS	1.03(0.97-1.10)	NS
Current or previous smoker	0.63(0.28-1.39)	NS	0.94(0.42-2.1)	NS	0.66(0.22-1.99)	NS	1.41(0.62-3.17)	NS	1.15(0.52-2.55)	NS
Number of comorbidities[c]	0.86(0.63-1.16)	NS	1.02(0.76-1.37)	NS	0.67(0.40-1.13)	NS	1.01(0.75-1.36)	NS	0.89(0.67-1.20)	NS
History or current evidence of concurrent osteoarthritis[d]	0.76(0.35-1.67)	NS	0.73(0.33-1.61)	NS	0.83(0.27-2.54)	NS	**0.41(0.18-0.93)**	**0.03**	0.70(0.32-1.52)	NS
RF positive	1.38(0.56-3.40)	NS	1.12(0.45-2.77)	NS	0.94(0.27-3.26)	NS	0.52(0.21-1.26)	NS	**0.37(0.14-0.97)**	**0.04**
ACPA positive	1.68(0.65-4.37)	NS	1.76(0.66-4.7)	NS	2.10(0.44-10.05)	NS	0.73(0.29-1.84)	NS	**0.36(0.13-1.00)**	**0.05**
SJC28	0.98(0.89-1.08)	NS	0.97(0.87-1.07)	NS	1.00(0.87-1.14)	NS	**0.85(0.75-0.96)**	**0.009**	**0.88(0.79-0.98)**	**0.02**
TJC28	**0.93(0.86-0.99)**	**0.03**	**0.90(0.83-0.97)**	**0.006**	**0.87(0.77-0.99)**	**0.04**	0.96(0.90-1.03)	NS	0.97(0.91-1.03)	NS
CRP, mg/L	0.99(0.98-1.00)	NS	0.99(0.98-1.00)	NS	0.99(0.98-1.01)	NS	0.99(0.97-1.00)	NS	**0.99(0.98-1.00)**	**0.03**
Patient VASDA, mm	**0.98(0.96-1.00)**[f]	**0.02**	0.98(0.97-1.00)[f]	NS	0.98(0.96-1.00)[f]	NS	0.99(0.97-1.01)[f]	NS	0.98(0.97-1.00)[f]	NS
DAS28-CRP3v	**0.66(0.45-0.97)**	**0.04**	**0.57(0.38-0.86)**	**0.008**	**0.53(0.30-0.95)**	**0.03**	**0.66(0.45-0.97)**	**0.04**	**0.59(0.40-0.87)**	**0.008**
HAQ	**0.46(0.23-0.93)**[g]	**0.03**	**0.46(0.23-0.95)**[g]	**0.04**	**0.28(0.10-0.79)**[g]	**0.02**	0.65(0.33-1.29)[g]	NS	0.49(0.24-1.01)[g]	NS
Total GS score on ultrasound[b]	1.00(0.96-1.04)[h]	NS	0.98(0.94-1.02)[h]	NS	1.00(0.95-1.05)[h]	NS	0.96(0.92-1.01)[h]	NS	0.97(0.93-1.01)[h]	NS
Total PDA score on ultrasound[b]	0.98(0.92-1.05)[h]	NS	0.97(0.91-1.04)[h]	NS	0.98(0.89-1.07)[h]	NS	**0.89(0.81-0.97)[h]**	**0.01**	**0.87(0.80-0.95)[h]**	**0.002**
Radiographic erosions	0.82(0.29-2.32)	NS	1.31(0.47-3.65)	NS	1.97(0.55-7.09)	NS	0.37(0.11-1.21)	NS	0.41(0.14-1.16)	NS

[a]2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA≤10mm). [b]Sum of GS or PDA semi-quantitative score assessed in 26 joints (GS or PDA graded between 0 and 3 for each joint, maximum total score 78). [c]Any of: hypertension, hypercholesterolaemia, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, asthma, chronic obstructive airways disease, diabetes, peptic ulcer disease, chronic kidney disease, chronic liver disease, epilepsy, demyelination, depression, thyroid dysfunction or cancer. [d]Osteoarthritis was defined according to a consultant rheumatologist diagnosis (i.e. symptoms and signs consistent with osteoarthritis). Missing data in [e]13, [f]27, [g]30 and [h]21 cases. Bold text indicates statistical significance at the level of p<0.05.
OR: odds ratio, CI: confidence interval, NS: not significant, BMI: body mass index, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, TJC: tender joint count, SJC: swollen joint count, CRP: C-reactive protein, VASDA: visual analogue scale global disease assessment, DAS28-CRP3v: disease activity score using 3 variables (SJC28, TJC28 and CRP), HAQ: health assessment questionnaire, GS: grey scale synovitis, PDA: power Doppler activity.

Table 5: Multivariable Analyses - baseline variables predictive of achievement of clinical and imaging outcomes at 12 months

Outcome at 12 months	Baseline Variable	OR (95% CI)	p	Missing Cases
DAS28-CRP4v<2.6	Symptom duration, months	**0.90(0.81-0.99)**	**0.04**	37
	TJC28	0.93(0.85-1.02)	NS	
	Patient VASDA, mm	0.98(0.95-1.00)	NS	
	HAQ	0.71(0.26-1.93)	NS	
DAS44-CRP4v<1.6	Female	**0.22(0.06-0.77)**	**0.02**	30
	Symptom duration, months	0.93(0.85-1.02)	NS	
	TJC28	**0.88(0.79-0.98)**	**0.02**	
	HAQ	0.53(0.23-1.26)	NS	
Boolean Remission[a]	Female	0.35(0.08-1.50)	NS	30
	TJC28	0.91(0.79-1.05)	NS	
	HAQ	**0.33(0.11-0.98)**	**0.05**	
Total PDA score[b]=0	History or current evidence of concurrent osteoarthritis[c]	**0.35(0.13-0.93)**	**0.04**	21
	SJC28	0.89(0.77-1.03)	NS	
	Total PDA score[b]	0.92(0.83-1.02)	NS	
Total PDA score[b]≤1	RF positivity	0.59(0.15-2.29)	NS	21
	ACPA positivity	0.54(0.14-2.07)	NS	
	SJC28	0.99(0.86-1.13)	NS	
	CRP	0.99(0.98-1.01)	NS	
	Total PDA score[b]	**0.89(0.81-0.98)**	**0.01**	

[a]2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA ≤10mm). [b]Sum of PDA semi-quantitative score assessed in 26 joints (PDA graded between 0 and 3 for each joint, maximum total score 78). [c]Osteoarthritis was defined according to a consultant rheumatologist diagnosis (i.e. symptoms and signs consistent with osteoarthritis). Bold text indicates statistical significance at the level of p<0.05. OR: odds ratio, CI: confidence interval, NS: not significant, TJC: tender joint count, VASDA: visual analogue scale global disease assessment, HAQ: health assessment questionnaire, SJC: swollen joint count, PDA: power Doppler activity, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, CRP: C-reactive protein.