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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.



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For Peer Review

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3 **Discordance between the predictors of clinical and imaging remission in patients with**
4 **early rheumatoid arthritis in clinical practice: implications for the use of ultrasound**
5 **within a treatment-to-target strategy.**
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36 **SHORT TITLE:** Implications for the use of US in early RA
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38
39 **ABSTRACT**

40
41 **Objective:** To assess the prevalence, relationship between and predictors of clinical and
42 imaging remission in early rheumatoid arthritis (RA), achieved with treat-to-target
43 management in clinical practice.
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46 **Methods:** A prospective observational study was conducted in patients with new-onset RA.
47 The treatment target was remission by disease activity score (DAS28-CRP<2.6). Twelve
48 month outcomes included DAS28-CRP remission, DAS44-CRP remission, ACR/EULAR
49 Boolean remission (BR) and absent or absent/minimal power Doppler activity (PDA) on
50 ultrasound (US) of 26 joints (total PDA score=0 or ≤1, respectively). Logistic regression was
51 conducted to identify baseline predictors of these outcomes.
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56 **Results:** Of 105 patients with complete 12-month data, the rate of DAS28-CRP remission
57 was 43%, DAS44-CRP remission was 39%, BR was 14%, absent PDA was 40% and
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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 \leq 3.3) or that developed using a Boolean approach: swollen joint count (SJC), tender

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

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

20
21 Ultrasound, by directly assessing the pathology of RA, may enable a more comprehensive
22 approach to defining remission which could guide therapeutic decisions. Imaging remission
23 has been proposed as a goal for therapy[14], supported by a recent study demonstrating a
24 superior rate of disease activity score (DAS44) remission at 18 months in patients receiving
25 treatment targeted to ultrasound remission in comparison to a target of DAS28 low disease
26 activity[15]. Further studies are proposed[16].

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

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

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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 \leq 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 \leq 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

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3 deranged liver function tests. Over 12 months, 9 (9%) and 20 (19%) patients failed treatment
4 with methotrexate or an alternative DMARD, respectively, due to intolerance or an adverse
5 event. Table 2 provides further details of patient management.
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8 The DAS28-CRP4v score was recorded at least every 3 months up to 12 months, or until the
9 target was met, in 76 (72%) patients. Escalation of DMARDs (excluding corticosteroids) was
10 appropriate (i.e. at least every 3 months if $\text{DAS28-CRP4v} \geq 2.6$) in 53/76 (70%) of these
11 patients. In a further 8 (10%) patients, corticosteroid therapy was escalated at least
12 3-monthly. Amongst the remaining 15 patients in whom treatment was not escalated despite
13 awareness of $\text{DAS28-CRP4v} \geq 2.6$, reasons throughout the 12 months were: awaiting effect
14 of previous treatment escalation (n=6), non-inflammatory symptoms only (n=5), acceptable
15 disease control (n=4), contraindication to treatment escalation (n=2), patient declined (n=2),
16 considered for biologic clinical trial (n=2) and isolated flare (n=1).
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22 As the target $\text{DAS28-CRP4v} < 2.6$ allows the presence of clinical swelling[28], there is still a
23 role for clinical assessment as recommended within EULAR guidelines. In fact, out of 158
24 visits at which $\text{DAS28-CRP4v} < 2.6$ was observed, DMARD treatment was escalated due to a
25 clinician impression of ongoing inflammatory disease activity at 26 (16%) visits.
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31 **Outcomes**

32 At 12 months, rates of DAS28-CRP4v remission ($\text{DAS28-CRP4v} < 2.6$) and low disease
33 activity ($\text{DAS28-CRP4v} < 3.2$) were 43% and 60%; rates of DAS44-CRP4v remission
34 ($\text{DAS44-CRP4v} < 1.6$) and low disease activity ($\text{DAS44-CRP4v} < 2.4$) were 39% and 73%.
35 The rate of 2011 ACR/EULAR Boolean remission was 14%. The thirty patients achieving
36 $\text{DAS28-CRP4v} < 2.6$ but not meeting the Boolean definition of remission missed the latter due
37 to patient $\text{VASDA} > 10\text{mm}$ (n=23), $\text{TJC} > 1$ (n=9), $\text{SJC} > 1$ (n=6) and/or $\text{CRP} > 10\text{mg/L}$ (n=6).
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42 In respect to ultrasound, absence of PDA (total PDA score=0) was observed in 42 (40%)
43 patients at 12 months. Absent/minimal PDA, defined by a total $\text{PDA} \leq 1$, was observed in 60
44 (57%) patients. If any low-grade PDA (grade 1) at the wrists and/or first MTP joints was also
45 accepted within the definition, seven additional patients achieved minimal PDA; i.e. 64% of
46 patients demonstrated a total PDA score ≤ 1 excluding $\text{PDA} = \text{grade 1}$ at individual wrist and
47 first MTP joints.
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51 Amongst 70 patients attaining $\text{DAS28-CRP4v} < 2.6$ at least once over the 12 months, the
52 median (IQR) time to first achievement of $\text{DAS28-CRP4v} < 2.6$ was 6 (3-9) months. In
53 patients achieving DAS28-CRP4v remission prior to month 12 (n=61), first DAS28-CRP4v
54 remission was sustained over the remaining follow-up in 27 (44%) patients. The majority of
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3 these patients achieved DAS28-CRP4v remission within the first 6 months; 41% and 70%
4 achieved remission by month 3 and month 6, respectively.
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8 **Agreement between Clinical and Imaging Outcomes**

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10 Prevalence and bias adjusted kappa statistics illustrate poor agreement between the clinical
11 and imaging outcomes (Table 3). In patients achieving the various definitions of clinical
12 remission at 12 months, absence of PDA (total PDA score=0) was observed in 19/45 (42%)
13 patients achieving DAS28-CRP4v<2.6, 18/41 (44%) patients achieving DAS44-CRP4v<1.6,
14 and 6/15 (40%) patients achieving Boolean remission. Absent/minimal PDA (total PDA
15 score≤1) was observed in 28/45 (62%), 27/41 (66%) and 10/15 (67%) patients, respectively.
16 With exclusion of low-grade PDA (grade 1) at the wrists and/or first MTP joints,
17 absent/minimal PDA was observed in 31/45 (69%) and 29/41 (71%) of patients achieving
18 DAS28-CRP4v and DAS44-CRP4v remission, respectively, whilst rate amongst patients
19 achieving Boolean remission was unchanged.
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23 In patients achieving DAS28-CRP4v<2.6 with ongoing imaging evidence of synovitis (n=26),
24 PDA was observed at the following sites: wrists (n=16), MCP2-3 (n=13), MTP1 (n=4), MTP2-
25 5 (n=4), PIP2-3 (n=4), elbows (n=2) and the knee (n=1). In patients achieving Boolean
26 remission the following joint regions were affected by PDA: MCP2-3 (n=5), wrists (n=4),
27 MTP2-5 (n=1), PIP2-3 (n=1), and elbows (n=1).
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31 In patients lacking any PDA, but with active disease as indicated by DAS28-CRP4v≥2.6
32 (n=23), median (IQR) values for the DAS28 component variables were TJC28 5(2-9), SJC28
33 1(0-2), patient VASDA 57(40-57) mm and CRP 9(0-18) mg/dL. Amongst 36 patients lacking
34 any PDA but not achieving Boolean remission, patient VASDA>10mm was the most frequent
35 preclusion to fulfilment of the Boolean criteria (n=32), followed by TJC53>1 (n=24),
36 CRP>10mg/dL (n=15) and SJC44>1 (n=9).
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46 **Predictors of Clinical and Imaging Outcomes**

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48 Univariable analyses demonstrated achievement of the various clinical remission outcomes
49 was significantly associated with male gender, shorter symptom duration, fewer tender joints
50 and lower HAQ at baseline (Table 4). In comparison, baseline parameters predictive of
51 achievement of imaging outcomes were lack of coexistent osteoarthritis, seronegativity,
52 fewer swollen joints, lower CRP and lower total PDA score on ultrasound. A lower
53 DAS28-CRP3v score at baseline was significantly associated with all outcomes. Excluding
54 PDA=grade 1 at the wrists and/or first MTP joints in the definition of absent/minimal PDA did
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3 not significantly affect the results, therefore only results for total PDA score ≤ 1 amongst all 26
4 joints are presented.

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6 Results of multivariable analysis, entering baseline variables demonstrating statistical
7 significance ($p < 0.05$) on univariable analysis, are shown in Table 5. The composite score
8 (DAS28-CRP) was assessed in univariable analyses, but not in multivariable analysis,
9 because of overlap with its component variables.
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12 13 **DISCUSSION**

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15 This large single-centre, contemporary study reveals that at 12 months almost half of
16 patients with new-onset RA achieve the clinical target (DAS28-CRP remission) in daily
17 practice, using EULAR treatment-to-target recommendations as a guide to management.
18 The rate of 2011 ACR/EULAR Boolean remission was significantly lower. In patients
19 achieving a state of clinical remission, regardless of the outcome measure used to define
20 remission (either DAS28, DAS44 or even 2011 ACR/EULAR Boolean remission), any PDA
21 (total PDA score > 0) was observed in at least half and significant PDA (total PDA score > 1)
22 was apparent in around one third of patients.
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26 The clinical remission rates are consistent with other observational treat-to-target RA cohorts
27 including the multicentre Dutch Rheumatoid Arthritis Monitoring (DREAM) cohort (DAS28
28 remission and 2011 ACR/EULAR Boolean remission observed in 58%[17] and 21%[38],
29 respectively) and an Italian early arthritis clinic (DAS44 remission in 46%)[19]. Methods of
30 assessment in the DREAM study included 28 joint examination and patient assessment of
31 general health, and it is not clear whether patients' global assessments of disease or more
32 extensive joint examination was available in the assessment of 2011 ACR/EULAR Boolean
33 remission. In the DREAM study, non-adherence to intensifying treatment in appropriate
34 patients was observed in 35% of visits, with the most frequent reasons being a physician
35 impression of clinical remission followed by side-effects[18], which is comparable to our
36 findings.
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40 Importantly, this is the first study to demonstrate the discordance between DAS28 remission,
41 or the more stringent 2011 ACR/EULAR Boolean definition of remission, and imaging
42 remission in early RA. It confirms findings previously reported in smaller studies of patients
43 with early RA achieving DAS44 remission using a DAS44-steered treatment protocol
44 (including methotrexate and TNF-inhibitor therapy): persistence of any PDA was identified in
45 42% of 48 patients amongst 10 joints (the wrists, second and third MCPs and PIPs)[39], and
46 41% of 43 patients using a 44-joint ultrasound assessment[12]. Other groups have reported
47 ongoing PDA in patients with established RA across various definitions of clinical remission
48 including DAS28[7, 8, 30, 40, 41], DAS44[10, 39] and 2011 ACR/EULAR Boolean-defined
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3 remission[7, 8], in the hands[7, 30, 39, 42, 43] or amongst more extensive joint
4 assessments[8, 10, 40, 41]. Issues of face validity of the clinical composite measures as
5 indicators of remission, which have previously been raised in established RA, are therefore
6 pertinent to early RA and the current recommended treatment strategy of targeting clinical
7 remission.
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10 A significant proportion of patients with absent or absent/minimal PDA had evidence of
11 clinical disease activity as measured by DAS28-CRP, DAS44-CRP and non-fulfilment of
12 2011 ACR/EULAR Boolean remission criteria. It is likely, at least for a subset of these
13 patients, that the standardised 26-joint ultrasound assessment missed active joint
14 inflammation in other joints (e.g. hips, shoulders, MCP3-5, PIP3-5). However, reduced
15 ultrasound joint assessments including the elbows, wrists, second and third MCPs, knees,
16 ankles and second to fifth MTPs have previously been shown to correlate well with
17 ultrasound assessment of 44 joints in both patients in clinical remission[40] and those with
18 active disease[44]. Moreover, the likelihood that the presence of tender joints and a high
19 patient global assessment which may be influenced by a complex interaction of factors other
20 than active synovitis (such as chronic pain, side-effects of treatment and the presence of
21 comorbidity) is also relevant, particularly given the characteristics which were evident in
22 these patients.
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31 Baseline predictors of clinical remission outcomes were male gender, shorter symptom
32 duration, fewer tender joints, and lower patient VASDA and HAQ scores. In contrast, lack of
33 osteoarthritis and objective signs of less severe disease (RF and ACPA negativity, fewer
34 clinically swollen joints, and lower CRP and baseline PDA) were associated with favourable
35 imaging outcomes. The latter parameters are arguably more reflective of the primary
36 pathology, active synovitis. Therefore, logically, they should warrant aggressive treatment or
37 treatment escalation if present or if increased above normal levels. These findings, therefore,
38 support current and future research into the use of imaging within the management of early
39 RA.
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45 The strengths of this study are its considerable size for a single-centre study. All assessors
46 were trained, supervised and working within one clinic, limiting variation in prescribing
47 behaviour. Management and data collection conducted in an out-patient clinic setting and
48 the absence of strict inclusion criteria afford a degree of generalisability to daily practice. Of
49 note, the prevalence of comorbidities was significant. Greater than one in ten patients in this
50 real-life cohort displayed a contraindication to commencement of methotrexate or intolerance
51 to it necessitating cessation. In addition, one in twenty patients failed an alternative DMARD
52 to methotrexate.
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3 Despite the planned prospective data collection, a proportion of patients were excluded due
4 to missing data, a significant drawback to this study method. The significantly higher SJC28,
5 TJC28 and RAI of patients with missing follow-up data in comparison to patients included in
6 analyses may be related to the proportion of patients who were subsequently referred to
7 biologics clinical trials or received biologic DMARDs with follow-up in biologics monitoring
8 clinic in which standardised ultrasound does not form part of routine assessments. Loss to
9 follow-up of patients with more severe disease may have falsely elevated the remission rates
10 observed. Limitations in the interpretation of PDA findings must be borne in mind, including
11 its validity in differentiating RA synovitis from findings in healthy joints[31, 32, 35, 41],
12 particularly in the wrist[32, 41], or those attributable to osteoarthritis[35-37]. Nonetheless,
13 prognostic validity of PDA in clinical remission has been demonstrated in relation to the
14 prediction of disease flare[10-12] and radiographic progression[9, 10].

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

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For Peer Review

Figure 1: Patient disposition.

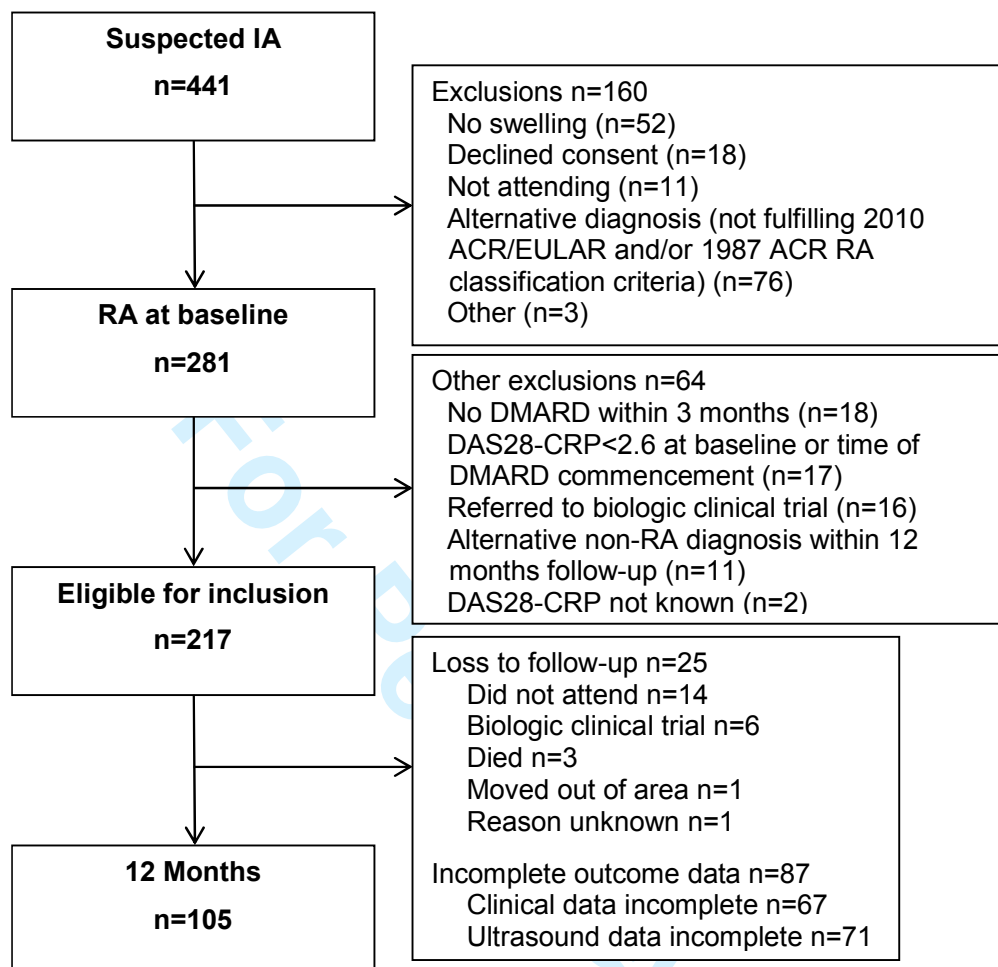


Table 1: Baseline characteristics

	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%)		
2	19 (18%)	-	31 (28%)	-	0.9
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

^aHypertension, 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. ^bOsteoarthritis was defined according to a consultant rheumatologist diagnosis (i.e. symptoms and signs consistent with osteoarthritis). ^cSum 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. ^a2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA≤10mm). ^bSum 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

^a2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA≤10mm). ^bSum 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). ^cAny 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. ^dOsteoarthritis was defined according to a consultant rheumatologist diagnosis (i.e. symptoms and signs consistent with osteoarthritis). Missing data in ^e13, ^f27, ^g30 and ^h21 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	

^a2011 ACR/EULAR Boolean remission (swollen joint count (SJC44) ≤1, tender joint count (TJC53) ≤1, CRP≤10mg/dL and patient VASDA ≤10mm). ^bSum of PDA semi-quantitative score assessed in 26 joints (PDA graded between 0 and 3 for each joint, maximum total score 78). ^cOsteoarthritis 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.