The predictive role of Ultrasound detected tenosynovitis and joint synovitis for flare in patients with Rheumatoid Arthritis in stable remission. Results of an Italian multicentre study of the Italian Society for Rheumatology Group for Ultrasound: the STARTER study.

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Abstract

Objective: to define the role of Ultrasound (US) for the assessment of patients with Rheumatoid Arthritis (RA) in clinical remission including joint and tendon evaluation.
Methods: a multicentre longitudinal study has been organised by the US study group of the Italian Society for Rheumatology. 25 Italian centres participated, enrolling consecutive patients with RA in clinical remission. All patients underwent complete clinical assessment (demographic data, disease characteristics, laboratory exams, clinical assessment of 28 joints, patient/physician reported outcomes) and Power Doppler (PD) US evaluation of wrist, metacarpo-phalangeal, and proximal interphalangeal joints, synovial tendons of the hands and wrists at enrolment, 6 and 12 months. Descriptive statistics were performed for all variables while the association between US variables and outcomes was evaluated through logistic regression. In addition, multivariate models were created. Study data were collected using Research Electronic Data Capture (REDCap). Analyses were performed using STATA software.
Results: 361 patients were enrolled, mean age of 56.19 (±13.31) years, 261 were female, with a mean disease duration of 9.75 (±8.07) years. In the 12-months follow-up, 98/326 (30.06%) patients presented a disease flare. The concurrent presence of PD positive tenosynovitis and joint synovitis predicted disease flare, with an OR (95% CI) of 2.75 (1.45,5.20) in crude analyses and 2.09 (1.06,4.13) in adjusted analyses. US variables did not predict the worsening of function or radiographic progression. US was able to predict flare at 12 months but not at 6 months.
Conclusions: PD positivity in tendons and joints predicts flare in patients with RA in clinical remission.

Introduction

Management of Rheumatoid Arthritis (RA) has changed dramatically the last 20 years thanks to early intensive treatment and the availability of new drugs. In order to assess disease activity, the European League Against Rheumatism (EULAR) recommends ultrasonography (US) for both assessing inflammatory activity and evaluating patients in remission as it can detect inflammation predicting subsequent joint damage[1].
On the other hand, the more recent EULAR recommendations for the management of RA[2], state that Boolean and index-based (SDAI, CDAI) definitions of clinical remission, should be used for defining disease activity and remission. Further, two recent studies that compared targeting sonographic remission with targeting clinical remission or low disease activity, aiming at imaging remission had no advantages, but had economic disadvantages[3,4]. However, such strategic trials in patients in clinical remission are lacking and there is no recommendation on the use of imaging in patients achieving clinical remission.
Muscolo-skeletal ultrasound (MSUS) can provide diagnostic and prognostic data in terms of risk of flare, disability and damage progression in RA[5–8]. Furthermore, MSUS allows the assessment of periarticular structures such as tendons, that could present inflammatory changes also in clinical remission[9]. In particular, the prognostic value of US tendon inflammation in patients in clinical remission is not known.
On this basis, the MSUS Study Group of the Italian Society for Rheumatology (SIR) prioritized its research activities on defining the role of US for the assessment of patients with RA in clinical remission, launching the Sonographic Tenosynovitis/arthritis Assessment in Rheumatoid Arthritis Patients in Remission (STARTER) study. The main objective of this study is to determine the prevalence of US tenosynovitis in RA patients in clinical remission and its association with unstable remission, function and damage. The secondary aim of the study is to assess joint synovitis and its association with flare, function and damage.

Methods

Patient and study design

This is a longitudinal analysis of the STARTER study, including 25 rheumatology centers. Selection criteria are fully described elsewhere[10]. Consecutive patients with RA (American College of Rheumatology (ACR) criteria 1987 [11] or ACR/EULAR 2010 criteria [12]) in clinical remission were recruited between October 2013 and June 2014. Remission was defined as: DAS28<2.6 [13], SDAI≤3.3[14], CDAI≤2.8[15], ACR/EULAR Boolean definition[16], absence of swollen/tender joints on 28 joints [17], remission based on clinical evaluation of an expert rheumatologist[18]. For the present analyses, patients with a baseline DAS28<3.2 were included. A secondary analysis in patients with DAS28<2.6 was performed for the primary and the functional outcome.
The study was approved by the local ethics committee of all sites. Written informed consent was obtained.

Clinical assessment
A full description of the clinical assessment is reported in the online supplement S1. Demographic (age, sex) and clinical variables (disease and remission duration, treatment), rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) were recorded at baseline. Clinimetric measures (the Italian version of the health assessment questionnaire (HAQ)[19], visual analogue scale for pain, physician global assessment, patient global assessment, global health), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 28-joint count were collected at baseline, 6 and 12 months by a rheumatologist blinded to US findings. Hands, wrists and feet plain radiographs were collected at baseline and 12 months. The Sharp van Der Hejide Score (erosion, joint space narrowing (JSN) and total score) was measured in pairs of radiographs by two external assessors, blinded to clinical and US findings.

Outcome measures
Disease flare, defined as change in DAS28≥1.2 or ≥0.6 if final DAS28>3.2[22], was the primary outcome.

Secondary outcomes included a change in the HAQ≥0.23[23] and the change in the Sharp van Der Hejide Score (total (Δ>4.3), erosion (Δ≥3) and JSN (Δ>2))[24]. For all outcomes, US variables were measured at baseline and outcomes evaluated at 12 months. A secondary analysis evaluated the impact of baseline US on flare at 6 months and the impact of 6 months US on flare at 12 months.

Ultrasonographic assessment

Ultrasonographers were rheumatologists expert in MSUS, selected by an inter- and intra-observer reliability exercise against a reference standard (AI) on static images using an e-learning platform. A good to excellent reliability (weighted kappa ≥0.7)[25] was required. Centers providing high level US machines (MyLab 70XVG, MyLab Twice, Logiq9, LogiqE9) with high frequency probes (14-18 MHz) were included. Esaote provided high-level US machines to investigators not having adequate US machines. MSUS following the EULAR guidelines[26] was performed by a single ultrasonographer blinded to clinical data at the baseline, 6 and 12 months.

A detailed description of the scanning protocol has been published previously[27], and is reported in the supplementary file S1. The flexors of the fingers, the flexor carpi radialis, the extensor tendons of the wrist were scanned bilaterally. The dorsal aspects of wrists (radiocarpal and midcarpal joints), metacarpophalangeal joints (MCP), and the palmar aspects of proximal interphalangeal joints (PIP) was scanned bilaterally.

Tenosynovitis, joint effusion and synovial hypertrophy were identified according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions[28]. Power Doppler (PD) assessment was performed under standardized settings (supplementary file S1). Representative images were recorded.

Grey scale (GS) and PD tenosynovitis (T) and synovitis (S) were semi-quantitatively scored from 0 to 3. Total scores for GS and PD T and S were obtained as the sum of single sites. An image atlas was distributed to the sonographers (supplementary material 2 and 3).

T and S were treated as categorical variables, defining their presence in case of GS or PD>1. To test the solidity of our results, alternative definitions were tested (GS>1, PD>1 for T and S).

Statistical analysis

Descriptive statistics were performed for demographic, clinical and US variables, reporting results as percentages, mean with standard deviation (SD) or median and interquartile ranges (IQR). Patients presenting a flare in the first six-month were compared to patients with a flare in the second six-month by Wilcoxon signed-rank test or Chi-square test.

The association between US variables and the outcomes was evaluated through logistic regression and results presented as OR and 95%CI, both crude and adjusted for pre-specified confounders (age, sex, disease duration, remission duration, musculoskeletal comorbidities, RF, ACPA, disease-modifying anti-rheumatic drugs (DMARDs), biologics, non-steroidal anti-inflammatory drugs (NSAIDs), systemic and local injected glucocorticoids) (supplementary file S1). To test the influence of treatment changes on flare, a secondary analysis adding a dichotomous variable on treatment decrease was performed.

To evaluate the additional impact of US and clinimetric variables on top of clinical findings, a model predicting the risk of flare including age, gender, disease duration, musculoskeletal comorbidities, RF and ACPA, remission duration (≤12 months or >12 months), DMARDs, biologics, steroid injections, NSAIDs was created, presenting the results as area under the curve (AUC) with 95% CI. Each single variable was added to the null model. Since some of the clinimetric variables are included in DAS28 and relate directly to the outcome, flare was also defined as intention to change treatment was tested; this definition was correlated with DAS28-defined flare by Pearson test.

Data were collected and managed using Research Electronic Data Capture (REDCap) [29]. Analyses were performed using STATA software package (2009, release 11; StataCorp, TX, USA).

Results

Demographic and clinical characteristics

A total of 361 patients were included, with a mean (standard deviation, sd) age of 56.19 (13.31) years, 261 (72.3%) were female, with a mean (sd) disease duration of 9.75 (8.07) years. The 283 patients with DAS28<2.6, had a mean (sd) age of 55.85 (13.55) years, 202 (71.3%) were females. Clinical and demographic features of both populations are presented in Table S4 (online only). After 6 months, 344 patients were still followed, while at 12 months 340. The clinical and US features at each time point are shown in Table 1.

		Baseline (361)	**6 months (344)**	**12 months (340)**
Age, years (mean, sd)		56.20 (13.31)		
Female/male (n,%)		261/100 (72.3/27.7)		
BMI (mean, sd)		24.42 (4.01)		
Current smokers (n, %)		65 (18.06)		
Disease duration, years (mean, sd)		9.75 (8.07)		
Remission duration, months (mean, sd)		20.30 (21.97)		
Extra-articular manifestation (n, %)		96 (26.59)		
MSK comorbidities (n, %)	***Fibromyalgia***	8 (2.22)		
	Osteoarthritis	74 (20.50)		
	Microcrystalline arthritis	3 (0.83)		
Erosions (n,%)		195 (54.32)		
sDMARDs (n,%)		276 (76.45)		
bDMARDs (n,%)		156 (43.21)		
Combination therapy (n, %)		91 (25.21)		
Corticosteroids (n, %)		163 (45.15)		
Joint injections in the previous month (n,%)		7 (1.94)		
NSAIDs (n, %)	***On demand***	198 (54.85)		
	Full dosage	6 (1.66)		
Anti-citrullinated peptide antibody positive (n, %)		207 (57.66)		
Rheumatoid factor positive (n, %)		201 (55.83)		
DAS 28 (mean, sd)		2.03 (0.68)	2.26 (0.92)	2.33 (0.99)
SDAI (median, IQR)		1.7 (0.7-3.5)	1.9 (0.5-5.1)	2.26 (0.71-5.33)
VAS PGA (median, IQR)		4 (0-13)	4.5 (0-20)	7 (0-17.75)
VAS EGA (median, IQR)		4 (0-10)	5 (0-12)	6 (0-16.5)
Swollen joint count (28 joints, median, IQR)		0 (0-0)	0 (0-1)	0 (0-0)
Tender joint count (28 joints, median, IQR)		0 (0-0)	0 (0-1)	0 (0-1)
ESR (median, IQR)		11 (5-18)	11 (6-19)	12 (6-20)
CRP (median, IQR)		0.07 (0-0.3)	0.1 (0-0.4)	0.1 (0-0.46)
VAS pain (median, IQR)		6 (0-16)	6 (0-20)	7 (0-20)
HAQ (median, IQR)		0 (0-0.38)	0.13 (0-0.38)	0.06 (0-0.38)
van der Heijde modifed Sharp score (median, IQR)		9 (3-28)		12 (4-40.5)
Erosion score (median, IQR)		1 (0-4)		2 (0-7)
Joint space narrowing score (median, IQR)		7 (2-21.75)		9 (2-32.5)
GS_T positive patients (n, %)		189 (52.35)	157 (46.18)	153 (46.79)
GS_T score in positive patient group (median, IQR)		2 (1-4)	3 (1-4)	3 (1-4)
GS_T positive tendons per patient (median, IQR)		1 (0-2)	0 (0-2)	0 (0-1)
GS_T score (median, IQR)		1 (0-3)	0 (0-2)	0 (0-2)
PD_T positive patients (n, %)		85 (23.55)	73 (21.47)	68 (20.80)
PD_T score in positive patient group (median, IQR)		2 (1-4)	2 (1-3)	2 (1-4)
PD_T positive tendons per patient (median, IQR)		0 (0-0)	0 (0-0)	0 (0-0)
PD_T score (median, IQR)		0 (0-0)	0 (0-0)	0 (0-0)
GS_S positive patients (n, %)		260 (72.02)	229 (67.35)	220 (67.28)
GS_S score in positive patient group (median, IQR)		3 (2-6)	3 (2-6)	4 (2-6.25)
GS_S positive joints per patient (median, IQR)		2 (0-4)	1 (0-4)	1 (0-4)
GS_S score (median, IQR)		2 (0-5)	2 (0-4)	2 (0-5)
PD_S positive patients (n, %)		161 (44.60)	134 (39.41)	132 (40.37)

PD_S score in positive patient group (median, IQR)	3 (2-5)	2 (1-4)	2 (1-5)
PD_S positive joints per patient (median, IQR)	0 (0-2)	0 (0-1)	0 (0-1)
PD_S score (median, IQR)	0 (0-2)	0 (0-2)	0 (0-2)
GS_T + GS_S positive patients (n, %)	292 (80.89)	256 (75.07)	240 (73.39)
PD_T + PD_S positive patients (n, %)	184 (50.97)	157 (46.18)	143 (43.73)
Patients with flare positive in US (any item)		53 (15.87)	57 (17.81)
Patients with positive US (any item) without flare		201 (60.18)	182 (56.88)

Table 1. Baseline, 6 and 12 month demographic, clinical and US features. MSK: musculoskeletal, DAS28: Disease Activity Score on 28 joints; sd: standard deviation; n: number; sDMARDs: synthetic disease modifying antirheumatic drugs; bDMARDs: biological disease modifying antirheumatic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; ACPA: anticitrullinated peptide antibodies; IQR: interquartile range; ESR: erythrosedimentation rate; CRP: C reactive protein; HAQ: Health Assessment Questionnaire; SDAI: Simplified Disease Activity Index, VAS: visual analogue scale; PGA: patients's global assessment; EGA: evaluator's global assessment; GS: grey scale; PD: power Doppler; T: tenosynovitis; S: synovitis; US: ultrasonographic.

Primary Outcome: disease flare

In the follow-up, 98/326 (30.06%) patients presented a flare. When comparing the 56 patients with a flare in the first six-month with patients with a flare in the second six-month (40 patients), there were no statistically significant differences in the demographic, clinical and clinimetric variables (Table 2). For two patients with flare at 12 months, the 6 months DAS28 was missing. Table 3 reports the clinical and US variables in patients with flare at baseline and at flare.

	Patients with flare at first 6 months (N=56)	**Patients with flare at last 6 months * (N=40)**	**P-value**
DAS 28 (mean, sd)	2.07 (0.77)	1.86 (0.79)	0.187
SDAI (median, sd)	2.4 (1 – 4.25)	2.2 (1.02 – 3.52)	0.572
Patient's global assessment of disease activity (median, IQR)	8 (2 – 15.25)	4 (0 – 12.25)	0.067
Investigator's global assessment of disease activity (median, IQR)	10 (0 – 15)	4 (0 – 11.25)	0.215
Swollen joint count (28 joints, median, IQR)	0 (0 – 1)	0 (0 – 0.25)	0.760
Tender joint count (28 joints, median, IQR)	0 (0 – 0)	0 (0 – 1)	0.322
ESR (median, IQR)	13 (4 – 23)	10 (2.75 – 15.25)	0.151
CRP (median, IQR)	0.02 (0 – 0.19)	0.09 (0 – 0.31)	0.297
Pain visual analogue scale (median, IQR)	10 (3.75 – 20)	4 (0 – 12)	0.0536
HAQ (median, IQR)	0 (0 – 0.63)	0.13 (0 – 0.5)	0.687
van der Heijde modified Sharp score (median, IQR)	11 (4 – 24.75)	10 (5 – 24)	0.584
Erosion score (median, IQR)	1 (0 – 4.25)	2 (0 – 4)	0.378
Joint space narrowing score (median, IQR)	7.5 (3 – 17.25)	8 (4 – 19)	0.573
GS_T positive patients (n, %)	31 (55.36)	27 (67.5)	0.323
GS_T positive tendons per patient (median, IQR)	0.12 (0.06 – 0.19)	0.12 (0.04 – 0.19)	0.8
PD_T positive patients (n, %)	14 (25.00)	13 (32.5)	0.565
PD_T positive tendons per patient (median, IQR)	0.12 (0.05 – 0.18)	0.08 (0.04 – 0.15	0.502
GS_S positive patients (n, %)	45 (80.36)	34 (85.00)	0.752
GS_S positive joints per patient (median, IQR)	0.18(0.09 – 0.36)	0.14 (0.09 – 0.32)	0.664
PD_S positive patients (n, %)	32 (57.14)	22 (55.00)	1
PD_S positive joints per patient (median, IQR)	0.14 (0.08 – 0.18)	0.11 (0.06 – 0.31	0.642

Table 2. Baseline clinical and ultrasonographic features in patients with disease flare in the first six-month and in the second six-month. Sd: standard deviation; IQR: interquartile range; HAQ: Health Assessment Questionnaire; US: ultrasonographic; GS: grey scale; PD: power Doppler. P-values calculated by Wilcoxon test, with the exception of US joints GS positive patients, US joints PD positive patients, US tendons GS positive patients, US tendons PD positive patients, for which Chi-Square test was used.

	Patients with flare at first 6 months	**Patients with flare at last 6 months**

	N=56		N=40		
	Baseline	**Flare**	**Baseline**	**6 months**	**Flare**
DAS 28 (mean, sd)	2.07 (0.77)	3.65 (0.83)	1.86 (0.79)	2.05 (0.75)	3.52 (0.88)
SDAI (median, IQR)	2.4 (1 – 4.25)	9.4 (5.48 – 13.64)	2.2 (1.02 – 3.52)	2.55 (0.9 – 5.03)	7.6 (4.75 – 11.92)
Patient's global assessment of disease activity (mean, sd – median, IQR – range)	11.07 (13.23) 8 (2 – 15.25) 0 - 65	28.88 (22.78) 26.50 (10.75 – 40) 0 - 95	7.25 (10.3) 4 (0 – 12.25) 0 - 50	11.22 (14.92) 5 (0 – 18.5) 0 - 71	27.45 (24.41) 18.5 (7.75 – 46.25) 0 - 78
Investigator's global assessment of disease activity (mean, sd – median, IQR – range)	9.89 (9.52) 10 (0 – 15) 0 - 36	26.66 (20.36) 20 (10.75 – 38.5) 0 - 79	6.98 (7.98) 4 (0 – 11.25) 0 - 30	8.25 (9.45) 5 (0 – 10.5) 0 - 35	22.5 (19.05) 20 (10 – 30) 0 - 82
Swollen joint count (28 joints, median, IQR)	0 (0 – 1)	1 (0 – 2.25)	0 (0 – 0.25)	0 (0 – 1)	1 (0 – 1)
Tender joint count (28 joints, median, IQR)	0 (0 – 0)	2 (1 – 4)	0 (0 – 1)	0 (0 – 0)	2 (1 – 3.25)
Erythrocyte sedimentation rate (median, IQR)	13 (4 – 23)	20.5 (12 – 33.25)	10 (2.75 – 15.25)	9 (4.75 – 18.25)	16.5 (9 – 31.5)
C-reactive protein (median, IQR)	0.02 (0 – 0.19)	0.1 (0 – 0.6)	0.09 (0 – 0.31)	0.11 (0 – 0.3)	0.3 (0 – 0.71)
Pain visual analogue scale (mean, sd – median, IQR – range)	13.11 (13.36) 10 (3.75 – 20) 0 - 65	27.57 (21.33) 28.5 (10 – 43.25) 0 - 80	9.38 (14.4) 4 (0 – 12) 0 - 80	15.75 (16.73) 10 (2.75 – 22.5) 0 - 60	26.92 (23.37) 20 (5.75 – 41.25) 0 – 75
HAQ (median, IQR)	0 (0 – 0.63)	0.38 (0 – 0.91)	0.13 (0 – 0.5)	0.13 (0 – 0.25)	0.13 (0 – 0.5)
van der Heijde modified Sharp score (median, IQR)	11 (4 – 24.75)	---	10 (5 – 24)	---	11 (7 – 33)
erosion score (median, IQR)	1 (0 – 4.25)	---	2 (0 – 4)	---	2 (0 – 6)
joint space narrowing score (median, I QR)	7.5 (3 – 17.25)	---	8 (4 – 19)	---	10 (6 – 19)
US joints GS positive patients (n,%)	45 (80.36)	48 (85.71)	34 (85.00)	31 (77.5)	32(82.05)
US positive GS joints per patient (mean , sd – median, IQR – range)	0.26 (0.23) 0.18(0.09 – 0.36) 0.05 – 1.05	0.30 (0.30) 0.18 (0.09 – 0.36) 0.05 – 1.14	0.27 (0.32) 0.14 (0.09 – 0.32) 0.05 – 1.68	0.23 (0.22) 0.18 (0.09 – 0.27) 0.05 – 0.95	0.26 (0.22) 0.18 (0.09 – 0.40) 0.05 – 0.73
US joints PD positive patients (n,%)	32 (57.14)	35 (62.5)	22 (55.00)	22 (55.00)	23 (58.97)
US positive PD joints per patient (mean , sd – median, IQR – range)	0.16 (0.15) 0.14 (0.08 – 0.18) 0.05 – 0.68	0.25 (0.24) 0.14 (0.09 – 0.34) 0.05 – 1.05	0.19 (0.16) 0.11 (0.06 – 0.31) 0.05 – 0.59	0.16 (0.17) 0.09 (0.05 – 0.22) 0.05 – 0.77	0.21 (0.22) 0.09 (0.05 – 0.25) 0.05 – 0.77
US tendons GS positive patients (n,%)	31 (55.36)	36 (64.29)	27 (67.5)	24 (60.00)	24 (61.54)
US positive GS tendons per patient (me an, sd – median, IQR – range)	0.16 (0.16) 0.12 (0.06 – 0.19) 0.04 – 0.69	0.14 (0.13) 0.08 (0.04 – 0.20) 0.04 – 0.65	0.17 (0.20) 0.12 (0.04 – 0.19) 0.04 – 1.04	0.13 (0.10) 0.10 (0.04 – 0.16) 0.04 – 0.35	0.18 (0.29) 0.10 (0.04 – 0.15) 0.04 – 1.42
US tendons PD positive patients (n,%)	14 (25.00)	19 (33.93)	13 (32.5)	10 (25.00)	12 (30.77)
US positive PD tendons per patient (me an, sd – median, IQR – range)	0.12 (0.08) 0.12 (0.05 – 0.18) 0.04 – 0.27	0.15 (0.15) 0.08 (0.04 – 0.25) 0.04 – 0.46	0.11 (0.10) 0.08 (0.04 – 0.15) 0.04 – 0.35	0.12 (0.07) 0.08 (0.08 – 0.17) 0.04 – 0.23	0.25 (0.31) 0.13 (0.08 – 0.22) 0.04 – 1.12

Table 3: main clinical and US measures at baseline and at flare. DAS28: disease activity score on 28 joints; sd: standard deviations; SDAI: simplified disease activity index; HAQ: Health assessment Questionnaire; IQR: interquartile range; US: ultrasonographic; GS: grey scale; PD: power Doppler.

In the overall population, the concurrent presence of PD t and S and GS T and S predicted disease flare, with an OR (95% CI) of 2.75 (1.45,5.20) in crude analyses and 2.09 (1.06,4.13) in adjusted analyses for PD, and of 2.88 (1.34,6.14) in crude models for GS, which was no longer statistically significant (2.25 (1.00,4.06)) when adjusted (Table 4, Figure 1).
In patients with DAS28<2.6, the concurrent presence of T and S significantly predicted flare in crude models for both GS and PD (OR 95%CI 2.59 (1.25,5.35) and 2.64 (1.17,5.96), respectively), but statistical significance was lost after adjustment (OR 95%CI 1.87 (0.85,4.12) and 1.94 (0.80,4.68), respectively).

	DAS28<3.2	**DAS28<2.6**

	OR (95%CI)	Adj OR (95% CI)	OR (95%CI)	Adj OR (95% CI)
PD-T	0.59 (0.16,2.15)	0.47 (0.12,1.82)	0.23 (0.02,1.82)	0.19 (0.02,1.67)
PD-S	1.64 (0.93,2.90)	1.59 (0.86,2.92)	1.4 (0.73,2.67)	1.42 (0.71,2.86)
PD-T + PD-S	***2.75 (1.45,5.20)***	***2.09 (1.06,4.13)***	***2.59 (1.25,5.35)***	1.87 (0.85,4.12)
GS-T	1.59 (0.53,4.72)	1.37 (0.42,4.41)	1.95 (0.59,6.41)	1.63 (0.43,6.07)
GS-S	2.18 (0.97,4.92)	1.88 (0.79,4.46)	1.99 (0.82,4.83)	1.74 (0.68,4.48)
GS-T + GS-S	***2.88 (1.34,6.14)***	2.25 (1.00,4.06)	***2.64 (1.17,5.96)***	1.94 (0.80,4.68)

Table 4: Odds Ratios and 95% CI for the occurrence of flare (increase of DAS28≥1.2 or ≥0.6 if final DAS28>3.2). Analyses adjusted for age, gender, disease duration, musculoskeletal comorbidities, RF positivity, remission duration, use of sDMARDS, bDMARDs, corticosteroids or NSAIDs. DAS28: disease activity score on 28 joints. PD: power Doppler; GS: grey scale; T: tenosynovitis; S: synovitis; OR: odds ratio; 95% CI: 95% confidence interval

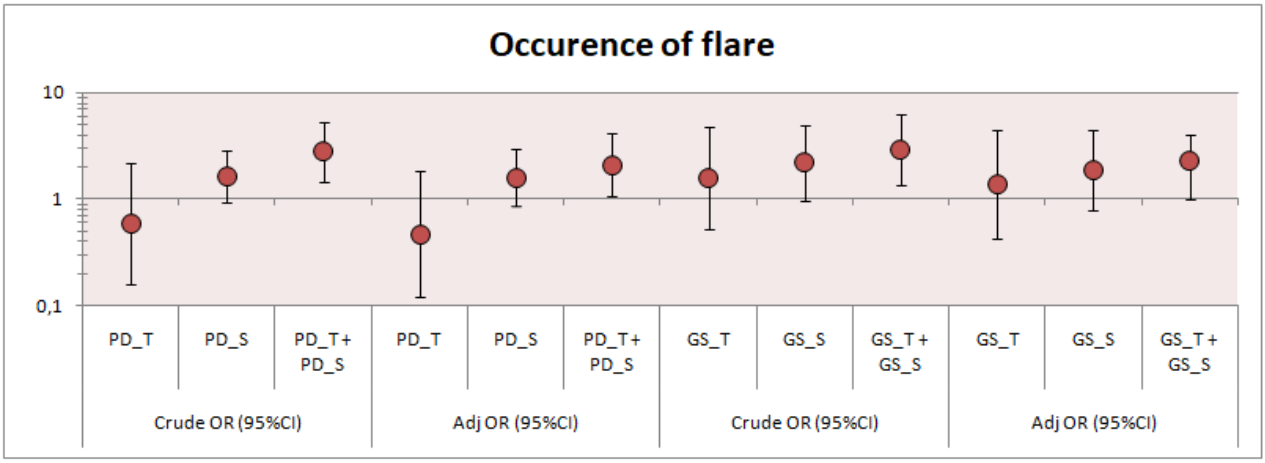

Figure 1: Odds Ratios and 95% CI for the occurrence of flare in the overall population. Adjusted for age, gender, disease duration, musculoskeletal comorbidities, RF positivity, remission duration, use of sDMARDS, bDMARDs, corticosteroids or NSAIDs. PD: power Doppler; GS: grey scale; T: tenosynovitis; S: synovitis; OR: odds ratio; 95% CI: 95% confidence interval.

Secondary Outcome: HAQ

In the follow-up, 70/340 (20.59%) of patients had a significant increase in the HAQ, 33 patients (14.47%) of the non-flare group and 35 (35.71%) in the flare group (p<0.001). In both cohorts, US variables did not significantly predict the worsening of function. (Table S5 and Figure S1 online only).

Secondary Outcome: Radiographic progression

For 189 patients, baseline and 12 month radiographs were available. At baseline, the median total SHS (IQR) was 24.52 (3-31), the median erosion score 1 (0-5) and the JSN score 8 (2-25). At 12 months 39/189 patients (20.63%) had a progression in the total score, 25/189 (13.23%) in the erosion score and 71/189 (37.57%) in the JSN score. The mean (SD) change of the total SHS score was 3.1 (8.28), 1.12 (3.6) for the erosion score and 1.91 (6.84) for JSN score. In the population of patients with DAS28<2.6 (157 patients with complete radiographic data), the median (IQR) baseline total SHS was 9 (2-28), while the scores for erosions and JSN were 1 (0-4) and 7 (2-23), respectively. At 12 months 34/157 (21.66%) patients had a progression in the total SHS score, 20/157 (12.74%) in the erosion and 59/157 (37.58%) in the JSN score. The mean (sd) change of the total SHS was 3.06 (6.42), 1.08 (3.7) and 1.98 (4.68) for the erosion and JSN scores, respectively. Patients with radiographic progression were equally distributed in the groups of patients with

and without flare (27 - 20.77% and 12 - 21.82 % respectively, p=1). None of the investigated US variables significantly predicted radiographic progression, also when erosion and JSN scores were examined separately (Table S6, Figure S2 online only).

Sensitivity analysis – stringent GS and PD definitions

More selective definitions for GS and PD were applied in patients with DAS28 <3.2. In crude and adjusted models, concurrent GS T and S predicted flare (OR (95% CI) 2.9 (1.2,7.05)). For PD, in both crude and adjusted models only the presence of isolated S predicted flare (OR (95% CI) 1.98 (1.02,3.81)). Three hundred forty patients were available to assess HAQ progression, but no US variable predicted a significant progression (Table S7, online only). For progression of the SHS, while in crude analysis GS S predicted progression of the erosion and JSN score, this was no longer significant when adjusted. In both crude and adjusted analyses the concurrent presence of GS T and S significantly predicted the progression of the JSN score (OR (95% CI) 5.28 (1.26,22.21)) (Table S8, online only)**.**

Sensitivity analysis – risk of 6 and 12 month flare

The risk of flare at 6 months based on baseline US and the risk of flare at 12 months based on 6 months US were calculated. In crude and adjusted models, flare at 6 months was not predicted by US variables. Conversely, flare at 12 months was predicted in both crude and adjusted analyses by PD S (OR, 95%CI 2.86 (1.3,6.33)) and GS T +S (OR, 95% CI 4.02 (1.37,11.82) (Table 5).

	Baseline US → 6 months flare		**6 months US→ 12 months flare**	
	OR (95%CI)	**Adj OR (95% CI)**	**OR (95%CI)**	**Adj OR (95% CI)**
PD-T	0.7 (0.15,3.21)	0.72 (0.15,3.44)	2.07 (0.62,6.94)	3.03 (0.83,11.07)
PD-S	1.84 (0.95,3.6)	1.78 (0.87,3.64)	***2.75 (1.31,5.77)***	***2.86 (1.3,6.33)***
PD-T + PD-S	1.77 (0.81,3.86)	1.3 (0.56,3.01)	2.27 (0.86,6.01)	1.79 (0.63,5.12)
GS-T	1.89 (0.53,6.76)	2.32 (0.59,9.12)	3.15 (0.76,13.02)	2.96 (0.67,13.07)
GS-S	2.43 (0.91,6.45)	2.82 (0.99,8.06)	2.76 (0.94,8.09)	2.67 (0.89,8.08)
GS-T + GS-S	2.13 (0.83,5.46)	1.88 (0.69,5.12)	***4.06 (1.46,11.26)***	***4.02 (1.37,11.82)***

Table 5: Odds Ratios and 95% CI for flare (increase of DAS28≥1.2 or ≥0.6 if final DAS28>3.2). Baseline US over the risk of flare at 6 months and 6 months US over the risk of flare at 12 months. Analyses adjusted for age, gender, disease duration, musculoskeletal comorbidities, RF positivity, remission duration, use of sDMARDS, bDMARDs, corticosteroids or NSAIDs. US: ultrasonography; GS: grey scale; T: tenosynovitis; S: synovitis; OR: odds ratio; 95% CI: 95% confidence interval.

Sensitivity analysis – treatment decrease

Analyses on the risk of flare at 12 months, predicted by baseline US variables, were repeated inserting a dichotomous variable on treatment decrease. With the addition of this variable, in adjusted models PD S (OR 95% CI 3.01 (1.36,6.63)) and GS T+S (OR 95% CI 3.86 (1.31,11.39) were still significant predictors of flare (Table S9, online only).

Application of US information in a clinical context

A weak but significant correlation was found between DAS28-defined flare and the intention to change treatment (rho 0.22, p<0.001). The AUC (95% CI) of the null model was 0.661 (0.598, 0.725) for DAS28 flare, 0.665 (0.556, 0.774) for treatment change. When adding US and clinical variables to the model, none of the

variables led to a relevant increase with both outcomes. An AUC >o.75 was obtained only with the addition of VAS pain (Table 6).

AUC (95% CI)	DAS28 flare	Change of treatment
Null Model	0.661 (0.598 – 0.725)	0.665 (0.556 – 0.774)
Null model + US		
GS_T	0.670 (0.608 – 0.733)	0.663 (0.555 – 0.772)
GS_S	0.674 (0.612 – 0.736)	0.679 (0.576 – 0.781)
PD_T	0.670 (0.606 – 0.733)	0.684 (0.580 – 0.788)
PD_S	0.690 (0.626 – 0.755)	0.716 (0.616 – 0.817)
GS	0.680 (0.618 – 0.742)	0.672 (0.568 – 0.777)
PD	0.690 (0.626 – 0.754)	0.720 (0.621 – 0.819)
Null model + clinimetric variables:		
VAS PGA	0.661 (0.598 – 0.724)	0.734 (0.644 – 0.824)
VAS EGA	0.686 (0.622 – 0.751)	0.668 (0.562 – 0.775)
VAS pain	0.661 (0.597 – 0.724)	0.768 (0.678 – 0.859)
VAS GH	0.661 (0.598 – 0.725)	0.698 (0.596 – 0.800)
Null model + joint count:		
SJC	0.665 (0.602 – 0.728)	0.668 (0.557 – 0.779)
TJC	0.661 (0.598 – 0.725)	0.690 (0.594 – 0.786)

Table 6: areas under the curve with 95% CI of the prediction models, defining flare as change in DAS28 (increase of DAS28≥1.2 or ≥0.6 if final DAS28>3.2) or as the intention to change treatment by the clinician. The null model includes age, gender, disease duration, musculoskeletal comorbidities, rheumatoid factor and anti-cyclic citrullinated peptides, remission duration, DMARDs, bDMARDs, steroid injections, NSAIDs. AUC: area under the curve; 95% CI: 95% confidence interval; DAS28: disease activity score on 28 joints; US: ultrasonographic; GS: grey scale; PD: power Doppler; T: tenosynovitis; S: synovitis; VAS: visual analogue scale; PGA: patient global assessment; EGA: evaluator's global assessment; GH: general health; SJC: swollen joint count; TJC: tender joint count.

Discussion

According to the latest EULAR recommendations, treatment of RA should aim at clinical remission [2], defined by clinical indices, to prevent joint damage and worsening of function. On the other hand, subclinical imaging-detected inflammation in clinical remission leads to flare and radiographic progression [5,7,30–32]. Further, clinical indices do not consider tendon involvement, which is frequent [33,34] and has an impact on disability [35]. Finally, the cross-sectional results of the STARTER study show the association between tenosynovitis and FLARE questionnaire in clinical remission [36].

The longitudinal analysis of the STARTER cohort confirmed that the conjunct presence of PD positive tenosynovitis and synovitis predict disease flare. While this result emerges consistently on the overall population, it is not confirmed when limiting the analyses to patients with DAS28<2.6, possibly because of a smaller sample and a baseline lower risk of flare. With more selective definitions for synovitis and tenosynovitis, a potential predictivity emerged also for GS. This is the first description of the impact of US-detected tenosynovitis in RA in clinical remission, highlighting a gap in the evaluation of disease activity, which is limited to joints. Taking also tenosynovitis into account could better drive therapeutic decisions, since the impact seems to be more relevant in patients in which treatment is tapered. In addition, patients

with positive PD have a higher risk of flare and should be monitored more tightly. This result was achieved defining clinical remission heterogeneously, in a multicenter study, using different US machines with different operators. While this might be regarded as a limitation, it probably implies a larger generalizability of the result, which is more likely to be reproduced in a clinical setting.

Regarding the secondary outcomes, US tenosynovitis or synovitis did not show any correlation with function worsening defined by the HAQ. This could be expected, as the sample size was powered to detect the primary outcome. The detection of a difference in patients that are not likely to progress rapidly would have required a larger sample as well as a longer follow-up.

The same considerations can be applied to the radiographic outcome, whose relevance has been questioned very recently[37,38], based on the reduction of its occurrence [39] and our population is not an exception.

Regarding the timing of US, in our study US predicts flare at twelve months but not at six. This suggests that in patients without any US inflammation, it could be useful to repeat US.

The addition of US and clinimetric variables to a model predicting flare did not lead to a relevant improvement of its performance. Neither swollen nor tender joint counts improved the prediction, and both counts, as well as acute phase reactants, remained substantially unchanged at flare, while greater changes were see in patient's reported outcomes. This aspect raises a further very important question: are the actual clinical indices adequate for defining remission and flare in all patients? In many of our patients, US did not reveal inflammatory exacerbation and flare was mainly PRO driven. It looks like the hot soup paradox of the Italian tradition: "who was burn with the soup blows also on the water".

The need for composite disease activity indexes emerged in the 90's and in a short period different indexes appeared [40][41]. All were meant to assess active disease but later emerged as a milestone in management [2]. Their thresholds for defining remission have been established [42] in randomized clinical trials and even in this context almost 10% of patients in DAS 28 remission had EGA and PGA scores compatible with active disease. In our cohort, comorbidities (with 20% of patients with osteoarthritis and 2% with fibromyalgia) could have interfered with the patient and physician's reported outcomes, shifting patients from stable to unstable remission.

US has demonstrated to be very sensitive in RA and its value has been acknowledged in the EULAR recommendations [1]. However, recent studies questioned the added value of US in guiding therapeutic decision [3,4], since US did not demonstrate to improve the outcomes, despite some possible methodological limitations [43]. Further, the role of residual US-detectable inflammation in clinical remission is still not clearly defined, considering that inflammatory changes can also be found in healthy subjects [44].

The STARTER study demonstrated that tendon and joint US can be useful in assessing inflammatory changes in RA in clinical remission to predict disease outcome and the impact of these findings on disease management should be tested in strategic trials.

On the other hand, in this cohort, disease flare is not always accompanied clinical and laboratory worsening but mainly by a change in the PROs, which might be influenced by comorbidities. In this scenario, US could confirm active disease and drive the therapeutic decision on top of composite indexes, in accordance with a

recent proposal by a group of US experts [45].

The research agenda on US in patients with RA in clinical remission is rich in unanswered questions regarding both the impact of PROs and the role of US. Decision making in RA should not be based on a single parameter and should be taken after acquisition of as much data as possible regarding not only the sensations of the patient but also objective and reliable data on disease activity. This is a doctor's job, not a machine's or a number's.

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1 Colebatch AN, Edwards CJ, Østergaard M, *et al.* EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013;**72**:804–14. doi:10.1136/annrheumdis-2012-203158

2 Smolen JS, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;:annrheumdis-2016-210715. doi:10.1136/annrheumdis-2016-210715

3 Dale J, Stirling A, Zhang R, *et al.* Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis* 2016;**75**:1043–50. doi:10.1136/annrheumdis-2015-208941

4 Haavardsholm EA, Aga A-B, Olsen IC, *et al.* Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. *BMJ* 2016;:i4205. doi:10.1136/bmj.i4205

5 Scirè CA, Montecucco C, Codullo V, *et al.* Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. *Rheumatol Oxf Engl* 2009;**48**:1092–7. doi:10.1093/rheumatology/kep171

6 Ten Cate DF, Luime JJ, Swen N, *et al.* Role of ultrasonography in diagnosing early rheumatoid arthritis and remission of rheumatoid arthritis-a systematic review of the literature. *Arthritis Res Ther* 2013;**15**:R4.

7 Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, *et al.* Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis. *Rheumatology* 2014;**53**:2110–8. doi:10.1093/rheumatology/keu217

8 D'Agostino M-A, Wakefield RJ, Berner-Hammer H, *et al.* Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. *Ann Rheum Dis* Published Online First: 20 November 2015. doi:10.1136/annrheumdis-2015-207709

9 Bruyn GAW, Hanova P, Iagnocco A, *et al.* Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. *Ann Rheum Dis* 2014;**73**:1929–34. doi:10.1136/annrheumdis-2013-203596

10 Bellis E, Scirè CA, Carrara G, *et al.* Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the Italian Society for Rheumatology. *Rheumatol Oxf Engl* 2016;**55**:1826–36. doi:10.1093/rheumatology/kew258

11 Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.

12 Aletaha D, Neogi T, Silman AJ, *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;**69**:1580–8. doi:10.1136/ard.2010.138461

13 Prevoo ML, van 't Hof MA, Kuper HH, *et al.* Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with

rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:44–8.

14 Felson D. Defining remission in rheumatoid arthritis. *Ann Rheum Dis* 2012;**71 Suppl 2**:i86-88. doi:10.1136/annrheumdis-2011-200618

15 Smolen JS, Breedveld FC, Schiff MH, *et al.* A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatol Oxf Engl* 2003;**42**:244–57.

16 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. *Ann Rheum Dis* 2011;**70**:404–13. doi:10.1136/ard.2011.149765

17 Scirè CA, Lunt M, Marshall T, *et al.* Early remission is associated with improved survival in patients with inflammatory polyarthritis: results from the Norfolk Arthritis Register. *Ann Rheum Dis* 2014;**73**:1677–82. doi:10.1136/annrheumdis-2013-203339

18 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**:2958–67. doi:10.1002/art.23945

19 Ranza R, Marchesoni A, Calori G, *et al.* The Italian version of the Functional Disability Index of the Health Assessment Questionnaire. A reliable instrument for multicenter studies on rheumatoid arthritis. *Clin Exp Rheumatol* 1993;**11**:123–8.

20 de Thurah A, Maribo T, Stengaard-Pedersen K. Patient self-assessment of flare in rheumatoid arthritis: criterion and concurrent validity of the Flare instrument. *Clin Rheumatol* 2016;**35**:467–71. doi:10.1007/s10067-014-2849-y

21 Berthelot J-M, De Bandt M, Morel J, *et al.* A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the “FLARE” instrument. *Ann Rheum Dis* 2012;**71**:1110–6. doi:10.1136/ard.2011.150656

22 van der Maas A, Lie E, Christensen R, *et al.* Construct and criterion validity of several proposed DAS28-based rheumatoid arthritis flare criteria: an OMERACT cohort validation study. *Ann Rheum Dis* 2013;**72**:1800–5. doi:10.1136/annrheumdis-2012-202281

23 Pope JE, Khanna D, Norrie D, *et al.* The minimally important difference for the health assessment questionnaire in rheumatoid arthritis clinical practice is smaller than in randomized controlled trials. *J Rheumatol* 2009;**36**:254–9. doi:10.3899/jrheum.080479

24 Bruynesteyn K, Van Der Linden S, Landewé R, *et al.* Progression of rheumatoid arthritis on plain radiographs judged differently by expert radiologists and rheumatologists. *J Rheumatol* 2004;**31**:1088–94.

25 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.

26 Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. *Ann Rheum Dis* 2001;:641–9.

27 Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the

Italian Society for Rheumatology.

28 Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino M-A, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005;**32**:2485–7.

29 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;**42**:377–81. doi:10.1016/j.jbi.2008.08.010

30 Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum. *Arthritis Rheum*;**58**:2958–67.

31 Molenaar ETH, Voskuyl AE, Dinant HJ, *et al.* Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004;**50**:36–42. doi:10.1002/art.11481

32 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**:792–8. doi:10.1136/ard.2010.134445

33 Filippucci E, Gabba A, Di Geso L, *et al.* Hand tendon involvement in rheumatoid arthritis: an ultrasound study. *Semin Arthritis Rheum* 2012;**41**:752–60. doi:10.1016/j.semarthrit.2011.09.006

34 Filippucci E, Garofalo G, Grassi W. Thumb troubles in rheumatoid arthritis. *Reumatismo* 2004;**56**:211–214.

35 Straub LR, Wilson EH. Spontaneous rupture of extensor tendons in the hand associated with rheumatoid arthritis. *J Bone Joint Surg Am* 1956;**38–A**:1208–1217; passim.

36 Bellis E, Scirè CA, Carrara G, *et al.* Ultrasound-detected tenosynovitis independently associates with patient-reported flare in patients with rheumatoid arthritis in clinical remission: results from the observational study STARTER of the Italian Society for Rheumatology. *Rheumatology* 2016;**55**:1826–36. doi:10.1093/rheumatology/kew258

37 van der Heijde D, Landewé R. Should radiographic progression still be used as outcome in RA? *Clin Immunol* Published Online First: July 2017. doi:10.1016/j.clim.2017.07.022

38 Landewé RBM, Connell CA, Bradley JD, *et al.* Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? Experience from tofacitinib clinical trials. *Arthritis Res Ther* 2016;**18**. doi:10.1186/s13075-016-1106-y

39 Rahman MU, Buchanan J, Doyle MK, *et al.* Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. *Ann Rheum Dis* 2011;**70**:1631–40. doi:10.1136/ard.2010.146043

40 Felson DT, Anderson JJ, Boers M, *et al.* The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993;**36**:729–40.

41 Smolen JS. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology* 2003;**42**:244–57. doi:10.1093/rheumatology/keg072

42 Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, Aletaha D, Allaart CF, Bathon J, Bombardieri S, Brooks P, Brown A, Matucci-Cerinic M, Choi H, Combe B, de Wit M, Dougados M, Emery P, Furst D, Gomez-Reino J, Hawker G, Keystone E, Khanna D, Kirwan J, Kvien TK, Landewé R, Listing J, Michaud K, Martin-Mola E, Montie P, Pincus T, Richards P, Siegel JN, Simon LS, Sokka T, Strand V, Tugwell P, Tyndall A, van der Heijde D, Verstappen S, White B, Wolfe F, Zink A, Boers M; American College of Rheumatology.; European League Against Rheumatism.. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011;**63**:573–86.

43 D'Agostino M, Boers M, Wakefield RJ, *et al.* Is it time to revisit the role of ultrasound in rheumatoid arthritis management? *Ann Rheum Dis* 2017;**76**:7–8. doi:10.1136/annrheumdis-2016-210453

44 Padovano I, Costantino F, Breban M, *et al.* Prevalence of ultrasound synovial inflammatory findings in healthy subjects. *Ann Rheum Dis* 2016;**75**:1819–23. doi:10.1136/annrheumdis-2015-208103

45 D'Agostino MA, Terslev L, Wakefield R, *et al.* Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. *Ann Rheum Dis* 2016;:annrheumdis-2016-209646. doi:10.1136/annrheumdis-2016-209646