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Original article

Superiority of SDAI over DAS-28 in assessment of remission in rheumatoid arthritis patients using power Doppler ultrasonography as a gold standard

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Abstract

Objective. To investigate the accuracy of composite scores in classifying RA patients who are in remission using the absence of inflammatory activity detected by ultrasound (US) as a gold standard.

Methods. Ninety-seven RA patients who were classified by their rheumatologists as being in remission were studied. Disease activity was assessed by the DAS-28 and simplified disease activity index (SDAI). US examination was performed in mode B and power Doppler (PD) in 42 joints.

Results. Synovial hypertrophy (SH) and PD were present in 92 (94.8%) and 41 (42.3%) patients. If we consider 'remission' to be the absence of joints with PD signal, no differences were found by DAS-28 between patients in remission and those not in remission, although differences were present by SDAI. We then calculated the sensitivity (S), specificity (Sp) and positive likelihood ratio (LR) of different SDAI cut-off points to predict absence of PD signal. SDAI < 5 had an S of 65% (95% CI 52, 76), Sp of 55% (95% CI 39, 69) and LR of 1.45 (95% CI 0.98, 2.15), whereas SDAI < 3.3 had an S of 57% (95% CI 44, 69), Sp of 74% (95% CI 58, 85) and LR of 2.24 (95% CI 1.25, 4.01).

Conclusions. Our results suggest that the SDAI classification of remission is closer to the concept of an absence of inflammatory activity, as defined by the absence of positive PD signal by US.

Key words: Rheumatoid arthritis, Remission, Composite scores, Ultrasonography.

Introduction

The introduction of new drugs and strategies capable of halting the inflammatory process associated with RA has increased the potential to achieve low levels of disease activity, and even remission. However, the definition of remission in RA is complex [1]. Remission should be the total absence of, or at most minimal, disease activity. However, objective criteria are required to accurately define this state, which is impossible to assess using routine clinical and laboratory examinations. But as remission can now be achieved [2], its measurement should permit the definition of a state that is as close as possible to the absence of disease activity and is suitable for use in clinical practice in order to prevent patients with low disease activity from remaining untreated.

Several definitions of remission have been proposed. One definition uses a categorical model, requiring criteria for several variables to be fulfilled (as the preliminary ARA criteria for remission) [3], and another uses a dimensional model, which integrates different disease activity measurements into pooled indices, creating scales that summarize different measurements into a single number [4]. Currently, the techniques most widely used to evaluate remission in clinical practice are composite scores, such as the disease activity score (DAS) or its modification for 28 joints (DAS-28) [5] and the simplified disease activity index (SDAI) [6]. However, even for composite indices, there are differences with regard to face validity as the frequency with which patients are classified as in remission is higher for the DAS-28 than for the SDAI [7, 8].

Advanced imaging techniques such as ultrasound (US) and MRI are playing an increasingly important role in the

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CLINICAL SCIENCE

demonstration and quantification of synovitis for assessment of inflammation in RA. This is important because synovitis represents a potential surrogate of disease activity [9]. Currently, US with power Doppler (PD) is being considered as an extension of the clinical examination because it provides direct visualization and assessment of synovitis [10], is relatively inexpensive, is non-invasive, allows one to achieve good representation of the patient's activity by imaging multiple joints in one session [11] and is useful for monitoring the response to RA therapy [12].

The persistence of synovitis has been demonstrated in patients fulfilling ARA and DAS criteria for remission both by US and MRI [13, 14], which may explain the progression of joint damage found in some patients in remission [15–17]. This suggests that some patients in clinical remission do not have an absence of disease activity, but rather exhibit a low level of inflammation that is not always easily detectable by clinical examination or reflected in laboratory results.

The aim of the present study was to examine the relationship between clinical remission and imaging remission in a large cohort of RA patients and to investigate the accuracy of the definition of remission, as defined by established criteria used in clinical practice. We aimed to define whether these indices may capture true differences in disease activity.

Material and methods

Patients and controls

This prospective study evaluated a cohort of 97 patients with RA, as defined by the ARA criteria [18], who attended the Rheumatology Outpatient Clinic at La Paz, University Hospital. Prior to inclusion, all patients provided informed consent to participate, and the study was approved by the Ethics Committee at our institution (Comisión de Etica de la Investigación Clínica del Hospital Universitario La Paz). A control group of 16 females from an osteoporosis outpatient clinic with no symptoms or signs of joint disease were also studied.

Patients were classified as being in clinical remission by their attending a rheumatologist using subjective clinical judgement, and were on DMARD therapy or biological agents. Other inclusion criteria were disease duration >12 months and no changes in treatment or significant disease flare in the past 6 months. Patients treated with a high dose of steroids (>7.5 mg of prednisone daily) or with a history of IA steroid joint injection during the past 6 months were excluded.

Demographic and clinical characteristics of each patient, including age, gender, age at disease onset, disease duration and current treatment with DMARDs were recorded at baseline. Patients underwent a complete clinical and laboratory assessment of disease activity using standard methods to calculate DASs, including the duration of morning stiffness, visual analogue scale (VAS), scores for joint pain, patient and physician global assessment of disease activity, number of tender and swollen joints using the 28 reduced articular index and functional capacity with the Spanish version of the HAQ [19]. Blood samples were collected to determine the ESR and levels of CRP. RF was measured by nephelometry (Behring, Nephelometer Analyzer II) with a detection limit of 15 U/ml, and anti-citrullinated peptide antibodies (ACPA) were determined using a second generation anti-CCP-2 antibody ELISA (Immunoscan RA Mark 2; Eurodiagnostica, Arnhem, The Netherlands) with a cut-off level of 25 arbitrary units/ml (AU/ml), according to the manufacturer's instructions. HLA class II alleles with the shared epitope [20] were determined by PCR.

Definitions of remission

Several definitions of remission were used in the study. First, patients were considered to be in clinical remission depending on the clinical judgement of the attending rheumatologist if the disease was under control without apparent signs of activity, and this was used as an inclusion criterion. Other established criteria included: modification of the preliminary ARA criteria for clinical remission [3], DAS-28 [21] or SDAI [22]. The original ARA criteria for clinical remission are attained when five of the following six criteria are fulfilled for at least 2 months: morning stiffness $\leqslant 15$ min; no fatigue; no joint pain by anamnesis; no joint tenderness or pain on movement; no joint swelling; and an ESR <30 mm/h for females or <20 mm/h for males. Modification of the ARA criteria consisted of exclusion of fatigue, as it is not assessed in routine clinical care. The assumption of lack of pain was based on a VAS pain score $\leqslant 10$ mm and no tender and swollen joints upon examination of reduced joint counts (0–28). A patient was considered to be in remission if four of the five criteria (excluding fatigue) were fulfilled at a single time point rather than over a consecutive 2 month period. Using DAS-28 and SDAI, two cut-off values were accepted as indicative of remission: for DAS-28, we selected the previously published value of 2.6 [21] and the newly proposed, stricter value of 2.4 [22]; for the SDAI, we used the previously proposed value of 5 and the new value of 3.3 [22].

Radiographic assessments

Standard postero-anterior radiographs of the hands and wrists and antero-posterior radiographs, including both forefeet, were obtained at the initial study consultation. One experienced reader (A.B.) scored all available radiographs for erosions.

Ultrasonographic examination

US examination was performed by an expert US rheumatologist (E.deM.) who was blinded to all other study findings. The equipment used was an Acuson Antares Siemens with a linear probe at 5–13 MHz and a Doppler frequency of 5–8.9 MHz. US examination for joint effusion and synovitis was carried out by grey-scale imaging, and synovial vascularization was assessed by PD in 42 joints: proximal IP, MCP, wrists, elbows, bilateral glenohumeral, knees, ankles, and midtarsal and MTP joints, according to OMERACT definitions of pathology [23].

Grey-scale imaging evaluation confirmed the presence or absence of synovial hypertrophy (SH) and/or joint effusion, which was graded using a semiquantitative scoring method consisting of a scale of 0–3, where 0 represented no SH, 1 mild hypertrophy, 2 moderate hypertrophy and 3 severe hypertrophy. PD was graded using a semiquantitative scoring method, which consists of a scale of 0–3, where 0 represented no PD signal, 1 one or two vessels in small joints or up to three single vessels in large joints, 2 less than half of the synovial area and 3 more than half of the synovial area. Scores were expressed per joint, and a total score was produced by addition of all joint scores.

Each patient evaluation took no more than 45 min, including documentation, and the images demonstrating maximal abnormalities were archived. Inter- and intraobserver reliability was determined by comparing the findings of two experienced rheumatologist ultrasonographers (EdM and C.C.) who independently read captured images in a random subset of 29 patients.

Statistical analyses

Inter- and intraobserver agreement in US findings were calculated by the intraclass correlation coefficient (ICC) and κ-statistics. Differences in US abnormalities between groups in remission or not with respect to normally distributed variables were analysed using a parametric test (Student's *t*-test), and non-normally distributed variables were analysed by the Mann–Whitney U-test. Correlation between disease activity variables and US abnormalities were analysed using the Spearman's or Pearson's correlation coefficient, depending on the variable distribution. Proportions were calculated by the chi-square test. Sensitivity (S), specificity (Sp) and odds ratio were calculated by 2×2 tables. A P-value <0.05 was considered statistically significant. Data were analysed using SPSS software (SPSS, Chicago, IL, USA).

Results

In total, 97 patients with RA were included in the study. Their demographic and clinical characteristics are shown in Table 1. The mean age was 56 years (range 18–82), and the mean disease duration was 5.9 years (range 1–18). All patients were being treated: 90 (92%) with classic DMARDs, 46 (47%) with MTX, 19 (20%) with LEF, 25 (26%) with several DMARD combinations and 7 (7%) with a DMARD in combination with an anti-TNF agent. The results of clinical and laboratory disease activity variables were low, as expected for patients in remission (Table 1). The mean DAS-28 score was 2.12 (range 0.29–4.49), and the mean SDAI was 7.7 (range 1–63.9). Seventy-four patients (76%) were in remission according to a DAS-28 score <2.6, and 65 (67%) when the stricter cut-off value of <2.4 was considered. Fifty-four (56%) patients were in remission according to a SDAI score <5, and this number fell to 43 (44%) when the most stringent cut-off of 3.3 was used. Seventy-three patients (75%) fulfilled the modified ARA criteria for remission. The correlation between DAS-28 and SDAI was only moderate ($r = 0.45$, $P < 0.001$).

Table 1 Demographic and baseline clinical characteristics of patients

Variable	Patients ($n = 97$)
Sex, female	70 (72)
Age, years	56.1 (12.2)
Disease duration, years	5.9 (9.6)
Patients treated with classic DMARDs	90 (92)
Patient pain assessment (0–10)	9.1 (12.3)
Patient global assessment (0–10)	8.5 (11.8)
Physician global assessment (0–10)	2.8 (6.2)
Tender joint count (0–28)	0 (range 0–3)
Swollen joint count (0–28)	0 (range 0–8)
ESR, mm/h	16.2 (10.3)
CRP, mg/dl	0.22 (IQR 0–2.4)
RF positive	62 (64)
ACPA positive	68 (70)
RF titres, IU/ml	35 (IQR 0–117)
ACPA titres, AI/ml	286 (IQR 0–1600)
DAS-28	2.12 (0.72)
SDAI	4.2 (1.2–8.8)
Presence of erosions in radiographs	70 (72)

Values are presented as mean (S.D.), median (range or IQR) and frequency (percentage)

Table 2 Ultrasonographic characteristics of patients ($n = 97$)

Number of patients with SH (28 joints)	85 (87.6)
Median number of joints with SH (28 joints)	3 (0–19)
SH score (28 joints)	3 (0–26)
Number of patients with SH (42 joints)	92 (94.8)
Median number of joints with SH (42 joints)	5 (0–28)
SH score (42 joints)	6 (0–36)
Number of patients with PD (28 joints)	35 (36.1)
Median number of joints with PD (28 joints)	0 (0–11)
PD score (28 joints)	0 (0–14)
Number of patients with PD (42 joints)	41 (42.3)
Median number of joints with PD (42 joints)	0 (0–11)
PD score (42 joints)	0 (0–14)

Data are presented as the number (%) or median (range).

Ultrasonographic findings

When 42 joints were considered, 92 out of the 97 RA patients displayed SH (94.8%) and 41 (42.3%) had a PD signal in at least one joint (Table 2). If only the 28 joints included in the reduced articular index were considered [24], 85 (87.6%) demonstrated evidence of SH and 35 (36.1%) displayed a PD signal. This means that if imaging was limited to only the 28 joints, 7 (7.2%) patients with SH and 6 (6.7%) with a PD signal would be lost (Table 2). In total, 4074 joints were explored by US among the 97 RA patients (Table 3). Of these, 588 (14.4%) demonstrated SH (545 grade 1, 42 grade 2 and 1 grade 3, according to the semiquantitative scoring method) and 99 (2.4%)

Table 3 Results of the US semiquantitative score for the 97 RA patients

	Score 0	Score 1	Score 2	Score 3
SH Score (42 joints)	3485 (85.5)	545 (13.3)	42 (1)	1 (0.002)
SH Score (28 joints)	2379 (87.5)	307 (11.3)	30 (1.1)	–
PD Score (42 joints)	3975 (97.5)	75 (1.8)	23 (0.6)	1 (0.002)
PD Score (28 joints)	2645 (97.3)	53 (1.9)	18 (0.7)	–

Data are presented as the number of joints (percentage over total number of examined joints). 42 joints = 4074 joints studied in total. Reduced joint count (28 joints) = 2716 joints studied.

had a PD signal (75 grade 1, 23 grade 2 and 1 grade 3). In the 28 joint counts, 2716 joints were explored (Table 3). Of these, 337 (12.4%) displayed SH (307 grade 1 and 30 grade 2) and 71 (2.6%) exhibited a PD signal (53 grade 1 and 18 grade 2).

Ultrasonographic findings in the control group

Among the 16 control females, 14 (87.5%) exhibited SH in at least one joint when the 42 explored joints were considered and 12 (75%) when the 28 joint count was used. Only 2 (12.5%) patients had evidence of a PD signal (in the wrists in both cases and thus captured in both 28 and 42 joint counts). In total, 672 joints were explored in the controls and, of these, 76 (11.3%) had SH (64 grade 1 and 12 grade 2). Only 3 (0.4%) demonstrated a PD signal: one control with PD in both wrists and one with PD only in the right wrist (all joints were scored as PD = 1). In the 28 joint count index, 448 joints were explored; of these 34 (7.5%) had SH (29 grade 1 and 5 grade 2) and 3 (0.7%) exhibited a PD signal.

The intra-reader ICC for the total Doppler score for reader 1 was 0.93 (95% CI 0.86, 0.96; $P < 0.001$); the ICC for the number of joints with a Doppler signal was 0.90 (95% CI 0.80, 0.95; $P < 0.001$); the ICC total score for SH was 0.71 (95% CI 0.48, 0.85; $P < 0.001$); and the Doppler intra-reader κ-correlation coefficient (CC) was 1. The inter-reader ICC for the total Doppler score was 0.92 (95% CI 0.84, 0.96; $P < 0.001$); the ICC number of joints with Doppler signal was 0.88 (95% CI 0.77, 0.94; $P < 0.001$); the ICC total score for SH was 0.58 (95% CI 0.27, 0.78, $P < 0.001$); the Doppler inter-reader κ-CC was 0.6 ($P < 0.001$).

Correlation of clinical and US variables

No correlation was found between clinical and laboratory variables and indices of disease activity based on the number of joints with SH or the total SH scores according to either 28 or 42 joint indices. However, a weak correlation was found between the number of swollen joints and the number of joints with a PD signal in the 28 joint count ($r = 0.23$, $P = 0.01$), the 42 joint count ($r = 0.23$, $P = 0.01$) and the PD score ($r = 0.24$, $P = 0.09$ in both articular indices). A correlation between the SDAI and the number of joints with a PD signal in the 28 and 42 joint counts ($r = 0.25$; $P = 0.007$ and $r = 0.27$; $P = 0.003$, respectively) and the PD score ($r = 0.26$; $P = 0.005$ and $r = 0.29$; $P = 0.002$, respectively) was detected. However, with the DAS-28, correlations were only observed with PD findings for 28 joint counts ($r = 0.17$, $P = 0.042$ for the number of joints with PD and $r = 0.17$, $P = 0.043$ with PD score). No correlation was found between ESR or CRP and PD. No differences in pathological findings obtained by US were found depending on the presence or absence of RF or ACPA or the HLA with the shared epitope.

Differences in US pathology depending on remission criteria

No significant differences were found between the number of US abnormalities, either in SH or the PD signal, and the ARA or DAS-28-defined remission status, although patients in remission, as defined by ARA or DAS-28 criteria, were more likely to have fewer joints with pathologies detected by US. Differences in PD signals were found for patients in remission or not, as defined by SDAI at both cut-off points (Table 4). These patients had fewer joints with a PD signal and a lower PD total score in both the 28 and extended joint counts (Table 4), and the differences were greater with the newly proposed cut-off point for remission of 3.3 (Table 4).

If we consider 'true remission' as an absence of joints with a PD signal, which reflects active synovial vascularization, and it is the upper quartile of PD findings among controls, we can compare disease activity between groups. No differences were found concerning DAS-28 between patients in remission and those with active disease as defined by US (2.07 ± 0.67 *vs.* 2.21 ± 0.79, respectively; $P = 0.49$), although differences were present in SDAI scores, with a median of 2.3 [interquartile range (IQR) 1–7.3] *vs.* 5.7 (IQR 3.1–10.6), $P = 0.007$. We then calculated the S, Sp and positive likelihood ratio (LR) (Table 5) for being in remission, as defined by SDAI. Patients in remission (SDAI < 5) displayed an S of 65.5%, Sp of 55% and LR of 1.45, while, with the cut-off point of 3.3, patients in remission had an S of 57.4%, Sp of 74.4% and LR of 2.24 (Table 5).

Discussion

To our knowledge, this is the first study to investigate the accuracy of the classification of remission by composite scores in RA patients using US imaging of a large number of joints. We have shown that a significant number of

Table 4 Differences in PD US findings depending on remission status defined by composite scores

	Remission ($n = 73$)	No remission ($n = 24$)	P
Modified ARA criteria			
PD score (28 joints)	0 (0–6)	0 (0–14)	0.132
Number of joints with PD (28 joints)	0 (0–4)	0 (0–11)	0.134
PD score (42 joints)	0 (0–8)	0 (0–14)	0.292
Number of joints with PD (42 joints)	0 (0–8)	0 (0–11)	0.252
	Remission ($n = 74$)	No remission ($n = 23$)	P
DAS-28 cut-off point 2.6			
PD score (28 joints)	0 (0–6)	0 (0–14)	0.379
Number of joints with PD (28 joints)	0 (0–4)	0 (0–11)	0.330
PD score (42 joints)	0 (0–8)	0 (0–14)	0.754
Number of joints with PD (42 joints)	0 (0–8)	0 (0–11)	0.746
	Remission ($n = 65$)	No remission ($n = 32$)	P
DAS-28 cut-off point 2.4			
PD score (28 joints)	0 (0–6)	0 (0–14)	0.316
Number of joints with PD (28 joints)	0 (0–4)	0 (0–11)	0.231
PD score (42 joints)	0 (0–8)	0 (0–14)	0.854
Number of joints with PD (42 joints)	0 (0–8)	0 (0–11)	0.758
	Remission ($n = 54$)	No remission ($n = 43$)	P
SDAI cut-off point 5			
PD score (28 joints)	0 (0–4)	0 (0–14)	0.044
Number of joints with PD (28 joints)	0 (0–4)	0 (0–11)	0.050
PD score (42 joints)	0 (0–8)	0 (0–14)	0.029
Number of joints with PD (42 joints)	0 (0–8)	0 (0–11)	0.037
	Remission ($n = 43$)	No remission ($n = 54$)	P
SDAI cut-off point 3.3			
PD score (28 joints)	0 (0–4)	0 (0–14)	0.006
Number of joints with PD (28 joints)	0 (0–4)	0 (0–11)	0.006
PD score (42 joints)	0 (0–8)	0 (0–14)	0.002
Number of joints with PD (42 joints)	0 (0–8)	0 (0–11)	0.003

Data are presented as median (range). All joints = 4074 joints. Reduced joint count (28 joints) = 2716 joints.

Table 5 Sensitivities, specificities and LR values for the definition of remission according to different SDAI cut-off points using an absence of joints with inflammation by PD signal as the gold standard

	Sensitivity (95% CI)	Specificity (95% CI)	LR (95% CI)
SDAI cut-off point 5	65.5 (52.3, 76.6)	55 (39.8, 69.3)	1.45 (0.98, 2.15)
SDAI cut-off point 3.3	57.4 (44.2, 69.7)	74.4 (58.9, 85.4)	2.24 (1.25, 4.01)

patients still have active synovitis, as detected by an increase in the PD signal, leading to two main conclusions: first, that a large number of joints needs to be explored by US to confirm the complete absence of synovial inflammation; and second, that remission, as classified by the SDAI, is the method that is closer to the concept of absence of inflammatory activity, as defined by the absence of a PD signal by US.

The term 'remission' is used to define a state that encompasses minimal or no disease activity [25]. To classify patients in remission, it seems reasonable to use the same instruments used to assess disease activity in clinical practice, but the use of various remission criteria and different cut-off points results in different degrees of disease activity being termed as remission [2]. Use of the DAS-28 tool to assess remission is most often discussed, since it permits evaluation of a large number of swollen joints and does not correspond to the absence of disease activity. It has been proposed that DAS or DAS-28 cut-off points should not be used to 'diagnose' remission [26]. SDAI scores correlate well with the DAS-28 results among patients with active disease, but only moderately well among patients in remission [7]. The SDAI cut-off point used to define remission is very stringent, allowing only a maximum of two swollen or painful joints, or one of each, to be present in remission. The criteria for remission are fulfilled by a smaller proportion of patients, and consequently the SDAI is not as prone to false positives

as the DAS-28 [8]. Both scores are useful in assessing moderate or high disease activity or therapeutic responses, and correlate with changes in sensible imaging techniques like US [12, 27].

A number of studies have reported the superiority of US over clinical evaluation for detecting joint inflammation [11, 28–32]. Our results confirm previous reports showing that US-detected active synovitis, which is often subclinical, is present in patients in clinical remission, although these studies were carried out using small numbers of patients or joints [11, 13, 14]. The strength of our study is that a large number of joints was studied, providing a total body synovitis score that reflects the overall disease activity. These results were then compared with composite scores used in clinical practice to classify patients in clinical remission.

Imaging of 42 joints most likely represents a patient's overall inflammatory activity and can be used as a gold standard for remission. A more comprehensive US assessment including a greater number of joints and multiple recesses [33, 34] could provide greater accuracy, but this comes at the cost of being more time consuming, making its use impossible for a significant number of patients. Therefore, joints not included in the assessment, like hips or subtalar joints, were found to exhibit a PD signal in $<$15% of active RA patients [32], and therefore these joints are unlikely to be commonly affected in patients in clinical remission. The fact that it takes 45 min to examine each patient, including documentation, suggests that this is not a feasible technique for use in routine clinical practice. US exploration of the 28 joints included in the reduced articular index [24] revealed that 7% of patients would have been misclassified as being in remission, and probably this number would increase with the use of simplified joint indices [34].

An US DAS-28 result has been shown to correlate well with the DAS-28 for patients with active disease beginning biological therapy [12]. In the present study, we showed that the correlation, although weak, persists in patients at the lower end of the inflammatory spectrum, but only when 28 joints are explored. The original DAS performs better than the DAS-28, specifically in classifying patients in remission, which may be a result of the weight of the variables included and the inclusion of more extended joint counts [26, 35]. However, the correlation of PD scores obtained from both 28- and 42-joint examinations were slightly better with the SDAI, supporting the conclusion that ankle and foot involvement is usually translated to a higher patient and physician global assessment or increased CRP levels, which result in higher SDAI scores [36].

SDAI has been proposed to be better than DAS-28 for assessment of remission because it correlates very well with the judgement of rheumatologists concerning disease activity. It also allows for an absence of any, or only minimal residual, disease activity [8]. Our results support these data, as we found significant differences in the number of joints with active synovitis when classifying patients as being in remission with the SDAI, as well as others [37], but not with the DAS-28. We also found differences by SDAI in the disease activity of patients with US defined remission.

Our study is the first to demonstrate the superiority of SDAI over DAS-28 in assessing remission in RA patients using the very stringent criteria of the absence of PD in a large number of joints as a gold standard. This limit, which represents the upper quartile in the findings for healthy controls, has biological face validity, but could be too strict, as PD can be detected in healthy controls [38] and OA patients [39, 40]. The origin of the signal can be investigated using colour Doppler US and the spectral Doppler Resistivity Index, which can differentiate between inflammatory and non-inflammatory disease and can be used as an indicator of RA inflammation [41].

The present study has several limitations. First, the inclusion criteria of remission as deemed by the rheumatologist seems to be practical, but there is a selection bias as there is likely a number of patients who are actually in DAS-28 remission, but were not included because the physician did not consider them to be remittive. Now, while residual disease activity is a commonly discussed concern with the DAS-28, in the case of this study the mentioned selection bias clearly is a disadvantage of the DAS-28. Secondly, US is an operator-dependent imaging technique, and its use in clinical practice implies that practitioners should have adequate training to achieve the necessary skills [42]. Therefore, in our study, US was performed by an experienced rheumatologist with $>$15 years of US practice. Thirdly, it is possible that MRI could demonstrate improved accuracy for detection of synovitis, as MRI with a contrast agent correlates well with clinical measures of inflammation [43] and allows quantification of synovial volume, which accurately reflects disease activity [44]. MRI interpretation may also affect the clinical significance of results, as the presence of bone oedema, which is not detected with US, may be a strong predictor of future erosions [45]. However, MRI is not a feasible technique for such a large number of joints and patients with the goal of obtaining an overall synovitis score.

In the present work, we demonstrated the superior performance of the lower cut-off point for SDAI in classifying patients in remission. Although this is to be expected, as lower cut-off points will include fewer swollen or tender joints and therefore lower assessments of disease activity, it also indicates that SDAI is able to capture some of the influence of residual disease activity, which can be present in subclinical synovitis in patients in clinical remission [11]. Further studies are required to assess whether these findings are also associated with clinically significant outcomes.

Rheumatology key messages

- The definition of remission in RA is complex and multiple definitions are used.
- To define remission, objective criteria are required as it is now a more achievable situation.
- SDAI classification of remission is closer to the concept of an absence of inflammatory activity.

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