

Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse

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Objectives. This study aimed to evaluate the usefulness of a systematic musculoskeletal ultrasonographic (US) assessment in the detection of residual disease activity in patients with early RA who achieved clinical remission.

Methods. We prospectively studied 106 early RA patients receiving conventional DMARDs according to a disease activity score (DAS)-steered therapeutic protocol over a 24-month period. Standard evaluation included clinical, laboratory, functional and systematic (44 joints) US assessment. US indexes of grey scale (GS) and power Doppler (PD) synovitis were correlated with clinical evaluation, laboratory indexes and clinical outcome. Clinical remission was defined when DAS was <1.6 at two consecutive visits 3 months apart.

Results. US examination was significantly more sensitive than clinical examination, both in active disease and in remission. In patients with an active disease, both clinical and US indexes correlated with CRP, whereas in remission only PD still remained significantly correlated. In clinical remission, 95% of the patients showed residual GS synovitis, and 41% of them showed a positive PD signal. Positive PD signal, even in a single joint, resulted the main predictor of relapse within 6 months, both in univariable and multivariable logistic regression analysis.

Conclusions. In a cohort of early RA patients treated with conventional DMARDs, US-GS can detect residual disease activity more sensitively than clinical examination both in active disease and in remission. Moreover, PD-positive synovial hypertrophy identifies an ongoing inflammation even during remission and predicts short-term relapse.

KEY WORDS: Ultrasonography, Doppler, Arthritis, Rheumatoid, Early diagnosis, Prognosis, Treatment outcome, Disease activity, Remission.

Introduction

Remission is the current aim of the treatment in RA [1]. Several clinical trials have demonstrated that clinical remission is a realistic end-point in RA allowing high remission rates, mainly in early RA [2–7].

Remission is ideally regarded as the absence of detectable disease and absence of structural and functional worsening over time [8, 9]. Practically, clinical remission is defined as absent or minimal disease activity, based on composite indexes including physician's and patient's judgement, clinical evaluation and laboratory indexes [10–13].

Even though several large perspective studies have shown that a sustained clinical remission status does not averagely associate with structural damage, some patients undergo structural and functional worsening, suggesting an apparent dissociation between disease activity and joint damage [8, 9]. Moreover, up to 52% of the patients who have achieved clinical remission undergo a disease exacerbation within 24 months suggesting that a residual inflammation may persist under a clinically detectable disease activity level [8].

Based on these considerations, it is critical to find measures that may predict a true disease remission both in terms of absence of radiological progression and persistent absence of joint inflammation.

Several efforts have been made to explain this subtle but relevant issue mainly advocating ultra-sensitive measures of joint inflammation, such as musculoskeletal ultrasonography (US) or MRI [14, 15].

US is more sensitive and reliable than clinical examination, and is better correlated with disease activity measures and structural damage progression [16–22].

In particular, US-detected joint effusion (JE) or synovial hypertrophy (SH) and power Doppler (PD) signal at multiple joint levels are valid disease activity markers in RA, modify after effective therapy and associate with a worsening in radiological scores both in established and early active RA [16, 18, 21, 23]. In established RA, US can also identify persistent inflammation even in patients in clinical remission [24–26].

Despite this evidence, it is not currently known whether a systematic ultrasonographic examination is useful in the assessment of clinical remission in patients with early RA as compared with standard clinical measures in terms of sensitivity, specificity and predictivity of short-term relapse.

To explore the usefulness of US in evaluating clinical remission in patients with early RA, we have investigated the relationship between clinical and US measures and between US indexes and acute phase reactants in a cohort of patients with early RA treated with a disease activity score (DAS)-steered tight control therapeutic protocol. Furthermore, we have evaluated the prognostic value of US parameters in terms of persistent remission vs early relapse.

Patients and methods

Patient recruitment

Three hundred and twenty patients from the cohort attending the Early Arthritis Clinic (EAC) of the Pavia University Hospital from September 2004 to October 2006 were screened. Referral criteria to the EAC included the presence of at least one of the following signs or symptoms for 6 weeks to 1 year of duration: (i) morning stiffness >30 min, (ii) swelling of three or more joints and (iii) swelling of less than three joints and positive squeezing test of metacarpophalangeal or metatarsophalangeal joints [27].

After careful differential diagnosis, all patients fulfilling the ACR criteria for RA [28] or presenting with a polyarthritis (PA) not further classifiable [undifferentiated PA (UPA)] evolving in

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Submitted 6 January 2009; revised version accepted 26 May 2009.

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RA during the follow-up were included in the study and prospectively evaluated for 24 months.

The study was approved by the local Ethical Committee of the IRCCS Policlinico San Matteo Foundation of Pavia. Patient's written consent was obtained according to the Declaration of Helsinki.

Patient assessment and treatment

One hundred and six patients underwent clinical evaluation at baseline and 2, 4, 6, 9, 12, 15, 18, 21 and 24 months. Ritchie's Articular Index (RAI), a 44-joint swollen joint count (SJC), patient global health assessment, HAQ, CRP, ESR and RF were measured at every visit. The original DAS was calculated for each patient at each time point [10]. Clinical remission was defined when DAS was <1.6 at two consecutive visits 3 months apart, after ≥ 12 months of follow-up. Relapse was defined as a DAS ≥ 1.6 following a period of clinical remission. The prognostic factors in UPA were scored according to Visser *et al.* [29]. A score ≥ 6 was considered as a poor prognostic index.

A tight control therapeutic protocol has been applied as follows: patients fulfilling RA criteria or UPA with poor prognostic factors ($n=3$) started with MTX 10 mg/week, whereas the remaining UPA patients started with HCQ 400 mg/day. If after 2 months the DAS was ≥ 2.4 , DMARD therapy was modified as follows: increase of MTX from 10 to 15 mg/week or from HCQ 400 mg/day to MTX 10 mg/week. At each following visit, MTX was escalated to a maximum dosage of 20 mg/week if DAS > 2.4 . Patients who did not reach DAS < 2.4 with the maximum tolerated MTX dosage started anti-TNF- α therapy. Steroid (prednisone 12.5 mg/day for 2 weeks and then 6.25 mg/day) was randomly assigned at baseline to half of the patients, as a part of an open-label therapeutic study on the efficacy of low doses of prednisone in early arthritis, approved by the local ethical committee.

Five RA and two UPA patients did not accept the therapeutic protocol at the study entry, and nine patients changed treatment during follow-up due to MTX-related liver enzyme increase (six patients) or steroid-related hyperglycaemia (two patients). All these patients had regular clinical and US evaluations, were included in the study and categorized by the baseline random assignment.

US protocol

After clinical examinations, US assessment was performed at baseline, and after 6, 12, 18 and 24 months by a single experienced operator, unaware of clinical data, using a Toshiba Nemio scanner with a multi-frequency linear array transducer (8–14 MHz), according to the European League Against Rheumatism (EULAR) guidelines [30].

The US assessment included bilateral shoulder, elbow, wrist (radiocarpal and midcarpal joint), MCP, PIP of the hands, sternoclavicular and acromioclavicular joint, knee, ankle and MTP joints.

The US protocol included transverse and longitudinal scanning of medial and lateral dorsal view of joint MCP, PIP and MTPs with joint in extension; longitudinal and transverse scanning of the dorsal aspect of the wrist (radio-carpal and mid-carpal joint) with joint in neutral position; longitudinal and transverse scanning of the supra-patellar recess, medial and lateral recesses of the knee in extension; longitudinal and transverse scanning of the anterior recess of the elbow, with joint in extended position; transverse scanning of the posterior recess of the gleno-humeral joint with the shoulder in neutral position; longitudinal and transverse scanning of tibio-tarsal joint with the ankle in extended position; longitudinal and transverse scanning of sternoclavicular and acromioclavicular joints.

Grey scale (GS) synovitis was defined as the presence of joint effusion and/or SH. The presence of JE/SH was

identified in each joint as abnormal anechoic/hypoechoic IA material according to the OMERACT definitions [31]. GS synovitis was subjectively graded from 0 to 3 (0=normal; 1=mild; 2=moderate; 3=marked) [32, 33]. The cut-off of normality for different joints was defined according to Schmidt *et al.* [34] taking into account that small effusion can be detectable even in healthy subjects. In particular, the maximum distance from the bony surface and the capsule was 2 mm for MCP, PIP, wrists, and 4 mm for knee according to Naredo *et al.* [21], and 3 mm for ankle, MTP, sterno-clavicular and acromio-clavicular.

Synovial PD was assessed by selecting a region of interest that included the bony margins, joint space and a variable view of surrounding tissues (depending on the joint size).

PD calibrations were adjusted at the lowest permissible pulse repetition frequency (PRF) to maximize sensitivity and were taken as constant for the same joint in different patients.

Doppler frequency was set higher for the study of small joints and superficial tissues, and lower for deep structures. Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts [35].

The PD signal was subjectively graded on a semi-quantitative scale from 0 to 3 (0=absence or minimal flow; 1=mild: single vessel signal; 2=moderate: confluent vessels; 3=marked: vessel signals in $>50\%$ of the joint area) on the image with the maximal enhancement on PD [21, 25, 35].

An overall US joint index for GS and PD signal was calculated at each US assessment as the sum of GS or PD signal scores obtained from each joint.

Each patient evaluation took ~ 60 min, and representative images were archived.

Inter-observer reliability was evaluated by comparing the findings of the two independent experienced rheumatologist ultrasonographers who performed US examinations of a series of 15 patients. Each examiner performed the US assessments independently and sequentially. Intra-observer reliability was assessed by blinded rescoring of the archived US images in the same subset 3 months after the respective real-time scanning.

Statistical analysis

Summary statistics of mean and s.d. or median and interquartile range (IQR), when appropriate, were presented for continuous variables. Differences between paired manually assessed SJC and US-joint count (JC) were analysed by paired *t*-test.

Spearman's or Pearson's correlation coefficients were computed to evaluate univariable associations among clinical, US and laboratory variables based on their distribution.

To compare the hierarchical relationship between clinical and US measures in the correlation with CRP, we performed a step-wise multivariate linear regression including SJC, RAI, US-JC and US-PD counts and scores. In such analysis, CRP values were square transformed due to their skewed distribution.

To assess the value of clinical (SJC, RAI, CRP and ESR) and US indexes (US-JC, US-GS score and US-PD count and score) at the time of remission as predictors of relapse during the following 6 months of follow-up, we performed receiving operating curves (ROCs) analyses.

The so-obtained best cut-off was applied to dichotomize variables to be included in a subsequent multivariable logistic regression analysis that explored the independent contribution of each variable in the prediction of clinical relapse.

Inter-observer and intra-observer agreement was calculated by an overall agreement (percentage of observed exact agreement), κ -statistics [unweighted for dichotomous scoring (e.g. presence/absence of synovitis); weighted for semi-quantitative scoring]

and intra-class correlation coefficients (ICCs). A k -value of 0–0.20 was considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent [36].

All statistical tests were two-sided and were performed at an α -level of 0.05. Statistical analyses were performed using the SPSS software (SPSS for Windows, Rel. 13.0. 2004, SPSS, Chicago, IL, USA).

Results

Patients' population

A total of 106 early RA patients were prospectively evaluated for a follow-up period of 24 months.

The main baseline clinical, laboratory and US characteristics of the early RA cohort are detailed in Table 1.

ACR criteria were fulfilled by 69% of the patients at baseline, whereas all other patients fulfilled ACR criteria for RA during the follow-up period. Roughly half of the patients were positive for RF (58/106) at 24 months, whereas only 39% were positive at baseline.

TABLE 1. Summary of baseline patients' characteristics

No. of patients	106
Age, mean \pm s.d., years	59.5 \pm 14.4
Sex, males:females	31:75
Disease duration, mean \pm s.d., months	3.8 \pm 2.8
ACR criteria, n	73/106
DAS, mean \pm s.d.	3.5 \pm 1
HAQ, mean \pm s.d.	1.2 \pm 0.8
SJC (44 joints), mean \pm s.d.	12.5 \pm 7.6
RAI, mean \pm s.d.	7.1 \pm 5.3
GH assessment (0–100), mean \pm s.d.	60.5 \pm 19.2
ESR, mean \pm s.d., mm/h	31.8 \pm 22.4
CRP, mean \pm s.d., mg/dl	1.9 \pm 2.4
RF positive, n (%)	41/106 (39)
ACPA positive, n (%)	30/103 (29)
Shared epitope, n (%)	35/93 (38)
Starting with MTX, n	72
Starting with HCQ, n	31
Starting with Prednisone, n	48

ACPA: anti-citrullinated peptide antibodies. GH: general health.

At the beginning of the study, all patients received DMARD therapy, mainly MTX (68%), and HCQ (29%). Two patients started with SSZ and one patient with CSA. Fifty-one patients were assigned to receive steroidal therapy.

After 12 months, 96 patients were treated with MTX (average dose 15 mg/week), three patients with adalimumab (40 mg every other week) plus MTX, three patients with SSZ (2 g/day), two with CSA (3 mg/kg/day) and two patients were not receiving DMARDs.

After 12 months of follow-up, 33 (35%) patients achieved clinical remission, and 10 additional patients achieved remission at 18 months.

US reliability

The inter-observer reliability assessment showed an exact agreement of 78 and 93% for the presence/absence of GS synovitis and for the PD signal, with $k=0.7$ and 0.8, respectively. Using the semi-quantitative grading system, the exact agreement was 62 and 86% for GS synovitis and for the PD signal, with weighted $k=0.6$ and 0.8 and ICC 0.8 and 0.9, respectively. The intra-observer reliability assessment showed an exact agreement of 86 and 98%, with $k=0.7$ and 0.9 for the presence/absence of GS synovitis and for the PD signal, respectively. Using the semi-quantitative grading system, exact agreement was 82 and 96%, with weighted $k=0.8$ and 0.9 and ICC 0.9, both for GS synovitis and PD signal, respectively.

Relationship between US and clinical or laboratory measures of disease activity

At baseline, US-JC showed a significant correlation with SJC ($r=0.7$, $P<0.001$) but it detected more involved joints than paired clinical examination (16.5 ± 9.7 vs 12.5 ± 7.6 , $P<0.001$). In remission, the difference became even more significant (6 ± 4.3 vs 2.6 ± 2 , $P<0.0001$) and the correlation decreased to 0.4 ($P<0.01$) (Fig. 1).

In clinical remission, 41 (95%) out of 43 patients showed persistent joint involvement by US-JC and 18 (41%) out of 43 showed a positive PD signal. In these cases, US-JC ranged

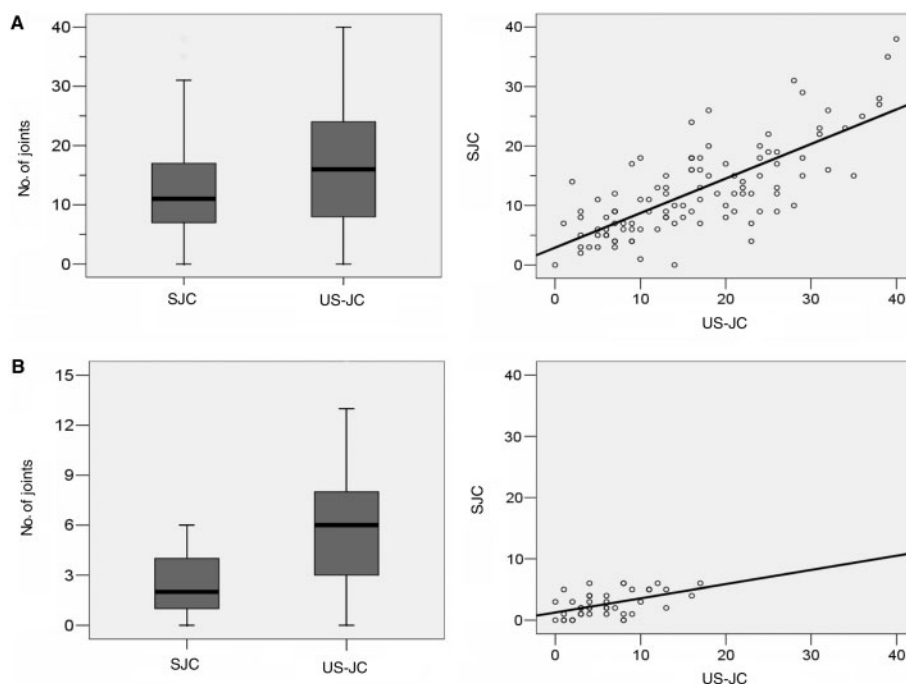


FIG. 1. Comparison and correlation between clinical SJC and US-JC in active disease (A) and in remission (B).

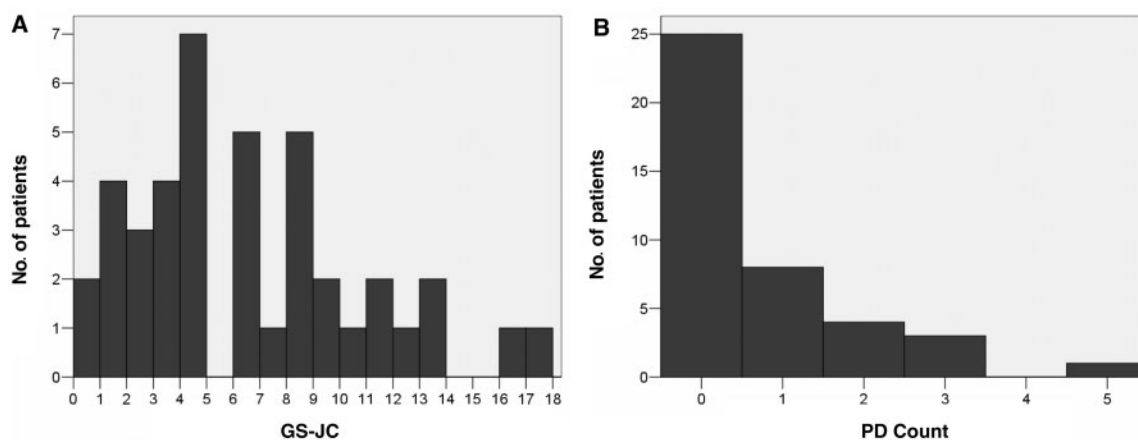


FIG. 2. Persistence of US-detected synovitis in early RA patients in clinical remission (A) GS synovitis and (B) PD synovitis.

TABLE 2. Correlations between clinical or US measures and disease activity indexes at baseline and in remission after 1 year

Parameters	Baseline		Remission	
	ESR	CRP	ESR	CRP
RAI	0.14	0.04	-0.14	-0.01
SJC	0.39 [§]	0.34 [§]	0.11	0.03
US-JC	0.41 [§]	0.32*	-0.04	0.08
US-GS score	0.44 [§]	0.37 [§]	-0.09	0.17
US-PD count	0.47 [§]	0.34 [§]	0.21	0.26*
US-PD score	0.43 [§]	0.36 [§]	0.21	0.28*

Spearman's ρ correlation coefficients are presented. [§] $P < 0.01$; * $P < 0.05$.

TABLE 3. Association between clinical and US findings at remission and the occurrence of clinical relapse within 6 months

	No relapse, $n = 29$	Relapse, $n = 14$	OR	95% CI
DAS > 1.1	13	11	9	0.7, 110.3
SJC > 1	13	9	0.6	0.1, 5.5
US-JC > 2	10	11	4.6	0.4, 49.5
US-PD > 0	5	12	12.8*	1.6, 103.5
Steroid	19	7	0.7	0.1, 4.4

The cut-off values were calculated by ROC curve analysis. * $P < 0.05$. OR: odds ratio.

from 1 to 17 (median value 6) and PD count from 1 to 5 (median value 1.5) (Fig. 2).

The correlations between clinical or US measures and ESR or CRP are reported in Table 2.

At baseline, both SJC and US indexes were significantly correlated with ESR and CRP, whereas in remission only PD measures are still found to be correlated with CRP.

Clinical and US predictors of sustained remission

Out of 43 patients achieving clinical remission, 14 showed disease relapse during the next 6 months. The DAS at remission was significantly higher in the patients who had a short-term relapse (mean 1.4 ± 0.2 vs 1 ± 0.3 , $P < 0.05$) as was the SJC [median (IQR) SJC 3 (2–6) vs 1 (0–3); $P < 0.05$]. Conversely, the number of tender joints, ESR and CRP did not differ between the two groups. Furthermore, the relapse rate was slightly lower in patients taking steroids, but this difference did not reach statistical significance (7/26 vs 7/17, $P = 0.51$).

PD count and US-JC were significantly higher in patients who relapsed: median (IQR) PD score 1 (1–2.5) vs 0 (0–0), and median (IQR) US-JC 6 (11–13) vs 2 (4–6.75) (all $P < 0.05$).

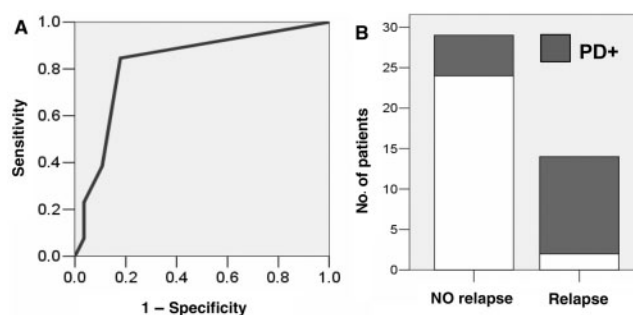


FIG. 3. PD-positive joints and occurrence of clinical relapse. (A) ROC curve for the number of involved joints. (B) Frequency of relapse according to the positive or negative PD status.

The cut-off values for each significant variable calculated from the ROC curves were: PD count > 0, US-JC > 2, DAS > 1.10 and SJC > 1. Based on these cut-off values, all variables were dichotomized and a multivariable binary logistic regression was performed.

The positivity of PD signal (at least at one site) resulted the main predictor of disease relapse in patients in clinical remission, even after adjustment for steroid medication (Table 3).

The area under the ROC curve for PD count was 0.8. A positive PD signal showed 85.7% sensitivity (95% CI = 57.2, 97.8) and 82.8% specificity (95% CI = 64.2, 94.1) for early relapse, with a positive predictive value of 70.6% and a negative predictive value of 92.3% (Fig. 3).

Discussion

In early RA patients who achieved clinical remission after a DAS-steered therapeutic strategy with conventional DMARDs, the results of the present study indicate that: (i) US is much more sensitive than clinical examination in the assessment of joint involvement; (ii) PD variables correlate with CRP in remission, whereas clinical parameters do not; and (iii) persistence of a positive PD signal in a single joint is the main independent predictor of early relapse.

Our study population included a homogeneous inception cohort of patients with early RA prospectively evaluated through the first 2 years of disease. Disease duration on average at the first evaluation was < 4 months, allowing ample opportunity to modify the disease course by an intensive therapeutic protocol [37]. The therapeutic strategy adopted in our cohort included a step-up DMARD titration followed by TNF- α inhibitors. None of the

patients who achieved clinical remission at 12 and 18 months had received TNF- α inhibitors. Therefore, all inferences about the quality of remission refer to a DMARD-induced remission.

Our definition of DAS-based remission is more stringent than the original one, requiring a remission status detectable at two consecutive visits after at least 1 year of DMARD therapy [10]. This reflects the need to exclude very short-lasting remissions or purely accidental low DAS calculations, in order to plan a possible step-down therapeutic strategy in those patients achieving remission. However, persistent PD signal and relapse are significantly associated when remission is calculated at a single time point (data not shown).

The remission rate we observed was similar to that reported in different RA cohorts treated with similar therapeutic strategies [2, 5, 37]. Relapse rate was 30% after 6 months in our series. This result is also consistent with data found in established RA [8].

Previous studies have indicated US as a good disease activity marker, sensitive to change after effective treatments [16, 21, 38, 39]. Our prospective study provides the first evidence of the predictive value of PD analysis in terms of sustained clinical response in patients with early RA. A recent study by Brown *et al.* [26] has indicated that PD associates with a 1-year radiological progression in clinical remission in established RA. On the other hand, persistent clinical remission is associated with a minimal radiological progression rate, whereas the most relevant characteristic associating with radiological progression is the concurrent exacerbation of RA [8].

Our data complete these findings, demonstrating that PD synovitis is a good predictor of unstable remission, which may explain the ongoing structural damage associated with a positive PD signal.

An important finding in our study is the high negative predictive value of the PD assessment. Indeed, a negative PD signal associates with stable remission in >90% of the cases supporting the concept that a more complete remission might be defined by a negative PD finding. Moreover, once a stable clinical remission has been achieved, we could speculate that a step-down therapeutic strategy might be limited to patients with a negative PD signal.

A new aspect arising from this study is the modification of the relationship between US and clinical parameters according to different disease activity levels. A systematic joint examination allowed a direct comparison between manual joint count and US joint count. The diminishing strength of the correlation between the manual joint count and US joint count in remission suggests that the former has a quite insensitive trend during the disease course compared with US as a measure of joint inflammation. Indeed, 95% of the patients in remission showed a US-JC > 0 and 41% had at least one positive PD signal by systematic joint assessment. These results in early RA are similar to those obtained in a cohort of established RA in DMARD-induced clinical remission by assessing hands and wrists: 73% of the patients showed a GS-SH and 43% a positivity of PD [25]. The higher values of GS synovitis in our cohort may be related to the higher number of joints evaluated (44 joints *vs* wrist/MCP joints), or to technical differences of the US equipment. In any case, the frequency of PD signal was comparable, suggesting that the most relevant joints for PD are included in wrists and MCPs. This is also supported by the evidence that a simplified US-PD evaluation is the predictive of radiographic progression in patients who achieved remission [26].

Thus, even though a direct validation of the best subset of joints to evaluate is not yet formally defined in patients in clinical remission, a simplified and less time-consuming joint count that includes wrist and MCP joints seems to be suitable for monitoring joint inflammation in this setting [26].

In our study, we also demonstrated a specific relationship of PD synovitis with an inflammatory index such as CRP. The strength of this correlation is quite weak and it should be regarded with caution. However, it is consistent with the generally accepted

view that PD is a specific marker of active synovitis, correlating with systemic inflammation [18, 40].

The present study does have some limitations. The first one is related to US analysis that can be regarded as poorly standardized and operator dependent. In our study, the OMERACT definitions of JE, SH and PD signal were adopted, and a wide joint assessment was performed in order to maximize the sensitivity in patients with very low disease activity. All patients were evaluated by the same operator, blinded to clinical data, who showed good to excellent intra-reader reliability for PD and GS indexes. Also inter-observer reliability scored good to excellent using this approach, suggesting that these results are reproducible in a routine clinical setting. Clearly, the machine-related sensitivity might affect reproducibility in terms of strength of the results if different technical equipment is employed.

A second limitation refers to the study population including at baseline both RA and UPA patients. One could speculate that stable remission is more likely in those presenting with UPA and that a positive PD signal is more likely in those presenting with RA, so that the inverse relationship between stable remission and positive PD signal might be spurious. As a matter of fact, lower PD activity and higher remission rate was found in those patients with UPA who did not develop RA criteria and who were excluded from the study (data not shown).

In our study population, ~70% of the patients fulfilled the RA criteria at baseline, and this finding was not independently associated either with the remission rate or with the percentage of PD positive synovitis.

In conclusion, our data support the specific role of US in detecting residual disease activity in early RA. PD-positive synovitis identifies subclinical synovial inflammation in a sensitive and specific way, and also predicts clinical outcome. Available data are now sufficient to test PD in therapeutic decisions, both as a marker of residual activity in patients achieving remission and as a marker of relapsing disease during a clinical remission period. PD monitoring in daily practice might lead to increase remission rates and to reduce disease relapses and structural damage progression of patients with early RA.

Rheumatology key messages

- Musculoskeletal US identifies subclinical synovitis in early RA.
- PD is specifically associated with ongoing subclinical inflammation.
- In clinical remission, PD signal predicts short-term relapse.

Disclosure statement: The authors have declared no conflicts of interest.

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