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Concise report

Grade and location of power Doppler are predictive of damage progression in rheumatoid arthritis patients in clinical remission by anti-tumour necrosis factor α

Bernd Raffeiner[1,2], Enrico Grisan[3], Costantino Botsios[1], Roberto Stramare[4], Gaia Rizzo[3], Livio Bernardi[1], Leonardo Punzi[1], Francesca Ometto[1] and Andrea Doria[1]

Abstract

Objectives. To investigate power Doppler (PD) signal, grade and location and their association with radiographic progression in RA patients in remission.

Methods. A prospective observational study was conducted in 125 consecutive RA patients in stable 28-joint DAS (DAS28) remission (⩾6 months) achieved on anti-TNF-α. At baseline, patients in stable remission underwent radiographic and US examination of the wrists and MCP, PIP and MTP joints. Semi-quantitative PD scoring (0–3) was recorded. We scored PD according to two locations: capsular or within synovial tissue without bone contact (location 1) and with bone contact or penetrating bone cortex (location 2). Radiographic progression was evaluated at the 1 year follow-up and defined as a change in van der Heijde–modified total Sharp score >0. Risk ratios (RRs) of radiographic progression according to presence, grade and location of PD were calculated.

Results. Four patients were excluded because of missing data. At baseline, 59/121 (48.7%) patients had a PD signal in one or more joints. PD location 2 was found in 74.6% patients (44/59). At the 1 year follow-up, 17/121 patients experienced radiographic progression: all had PD signal in one or more joints at baseline (RR 2.47, $P < 0.0001$). Radiographic progression was associated with the following baseline US features: PD grade 2 (RR 4.58, $P < 0.01$), PD grade 3 (RR 3.49, $P < 0.05$), total PD score ⩾2 (sum of all PD scores) (RR 3.19, $P < 0.0001$) and PD location 2 (RR 3.49, $P < 0.0001$).

Conclusion. Higher PD grades and PD in contact with/or penetrating bone are associated with radiographic progression in patients in DAS28 remission.

Key words: rheumatoid arthritis, power Doppler, power Doppler location, power Doppler grade, remission, radiographic progression, ultrasound, erosion, synovitis, anti-TNF-α agents

CLINICAL SCIENCE

Rheumatology key messages

- Almost half of RA patients in DAS28 remission have positive power Doppler signal.
- Higher power Doppler grades are associated with radiographic progression in RA.
- Power Doppler signal in contact with or penetrating bone is associated with radiographic progression in RA.

[1]Rheumatology Unit, Department of Medicine – DIMED, University of Padova, Padova, [2]Rheumatology Unit, Department of Medicine, Central Hospital of Bolzano, Bolzano, [3]Department of Information Engineering and [4]Radiology, Department of Medicine – DIMED, University of Padova, Padova, Italy

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Correspondence to: Bernd Raffeiner, Rheumatology Unit, Department of Medicine – DIMED, University of Padova Via Giustiniani 2, 35128 Padova, Italy.
E-mail: berndraffeiner@yahoo.com

Introduction

The validity of US findings in predicting structural and clinical outcomes in RA has gained increasing interest in recent years, especially with regard to the assessment of remission [1]. Joint inflammation detected by US is common in patients in clinical remission [2–4]. In patients treated with conventional DMARDs, US synovitis has already proved to be predictive of radiographic progression at the 1 year follow-up, while no association has been found with baseline clinical variables [5, 6]. TNF-α blockers directly inhibit osteoclastogenesis [7] and are highly effective in blocking radiological damage, even at half dose if remission is stable [8]. The association of US synovitis with damage progression in RA patients in remission achieved on TNF-α blockers has not yet been studied.

The aim of our study was to investigate the rate of active synovitis, defined as the presence of synovial power Doppler (PD) signal, in patients in remission induced by TNF-α blockers and to assess the grade and location of PD signal. Furthermore, we analysed the association of PD signal, PD grade and PD location with radiographic progression.

Methods

A prospective observational study was performed in 125 consecutive RA patients on TNF-α blockers, who were in stable (⩾6 months) 28-joint DAS (DAS28) remission [9] between January 2012 and December 2014. The study was carried out in accordance with the Declaration of Helsinki (1983). The study was approved by the ethics committee for the clinical trials of the province of Padova and all patients signed an informed consent.

Demographic, clinical and laboratory variables and treatment information of the patients were collected at baseline. Patients were assessed every 3 months. In case of disease relapse (DAS28 ⩾ 2.6 on two consecutive visits), the patient was excluded from the study.

At baseline, US examination of MCP joints, PIP joints, wrists (inter- and radiocarpal) and MTP joints was performed with a multiplanar technique in the dorsal view according to the EULAR guidelines for musculoskeletal US [10]. US examinations were performed using MyLab 70 XVG (Esaote Biomedica, Genoa, Italy) equipped with a 6–18 MHz broadband multifrequency linear transducer (axial resolution = 30 μm, lateral resolution = 60 μm) and Doppler frequency ranging from 7.1 to 14.3 MHz.

Active synovitis was identified by a positive PD signal in the synovial tissue. The number of joints with a PD signal was recorded, together with the semi-quantitative PD scoring, ranging from 0 to 3 [5]. The PD grade of each patient was defined according to the highest PD grade found in the assessed joints. A total PD score was calculated as the sum of PD scores in all the examined joints of each patient. A cut-off of a total PD score ⩾2 was adopted. The location of a PD signal in the synovial tissue was scored as follows: capsular or within synovial tissue without bone contact (location 1) and with bone contact or penetrating bone cortex (location 2) (Fig. 1). The PD location of each patient was defined as location 2 if location 2 was found in at least one joint, otherwise the PD location was defined as location 1.

All patients underwent hands and feet radiographs at baseline and at the 1 year follow-up. Radiographic progression was defined as a change in van der Heijde–modified total Sharp score ($\Delta TSS > 0$). Clinical assessment, US and radiographs examination were performed by three investigators blinded to each other (C.B., B.R. and R.S.). A fourth blinded investigator (L.B.) re-examined the US images to score PD locations.

The association of continuous variables with radiographic progression was tested with exact permutation distributions. The association of categorical variables with radiographic progression was expressed as the risk ratio (RR) of radiographic progression assessed using two-tailed Fisher's exact test. Interreader reliability with regard to the PD location was assessed using Cohen's κ. To test the ability of US variables to predict the amount of radiological progression, $d\widehat{\Delta TSS}$, a generalized linear regression model was used. The model estimates the coefficients w_i to combine the input variables as follows:

$$\widehat{\Delta TSS} = w_0 + \sum_{i=1}^{N} w_i x_i + \sum_{\substack{i,j=1 \\ i \neq j}}^{N} w_{ij} x_i x_j$$

The following variables were included: PD signal in one or more joints, PD grade, number of joints with PD signal, PD location and total PD grade. A stepwise regression estimation method was used.

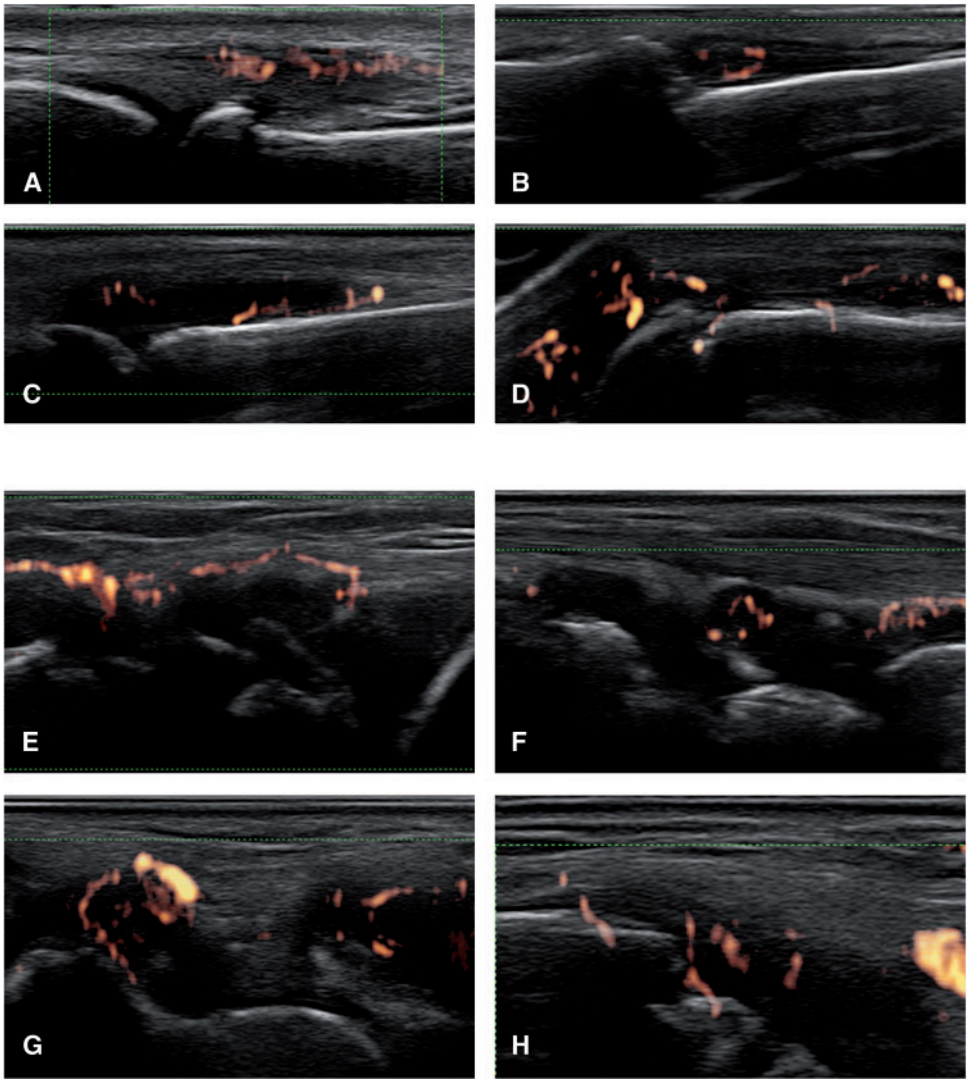
Statistical analysis was performed using MATLAB 2014b (MathWorks, Natick, MA, USA).

Results

None of patients experienced a disease relapse and was excluded from the study. We included 121/125 patients who had a complete baseline assessment and 1 year radiographic follow-up. Characteristics of patients and treatments are reported in Table 1.

At the baseline US evaluation, all patients had synovial hypertrophy in one or more joints and almost half of the patients [48.7% (59/121)] had a positive PD signal. A PD signal was observed in one joint in 64.4% (38/59) of the patients. The maximum number of joints with a PD signal at baseline was eight. Among the 4114 analysed joints (10 MCPs, 10 PIPs, 4 wrists and 10 MTPs per patient), 94 (2.3%) had a PD signal: 92.4% (87/94) in the hands, 63.8% (60/94) in the wrists, 21.2% (20/94) in the MCP joints, 7.5% (7/94) in the PIP joints and 7.5% (7/94) in the MTP joints. The mean total PD score was 1.1 (SD 1.7), and 35 (28.9%) patients had a total PD score ⩾2. The maximum PD grade was 3 in 11/59 (18.6%) patients. The majority of PD signals [44/59 (74.6%)] was in location 2, with bone contact or penetrating bone cortex (Table 1). The interreader agreement for PD location was very high

Fig. 1 Classification of PD location



Location at the MCP level (**A**–**D**) and at the wrist level (**E**–**H**). Location 1: (**A** and **E**) capsular or (**B** and **F**) within synovial tissue without bone contact; location 2: (**C** and **G**) with bone contact or (**D** and **H**) penetrating bone cortex. Power Doppler location of each patient was defined as location 2 if location 2 was found in at least one joint, otherwise the PD location was defined as location 1.

(Cohen's $\kappa = 0.91$). The mean PD grade in patients with location 1 was 1.8 (S.D. 0.8) and 1.1 (S.D. 0.3) in patients with location 2 ($P < 0.001$).

Only 17/121 (14.1%) patients experienced radiographic progression after 1 year. The mean ΔTSS in the 17 patients who progressed was 1.1 (S.D. 1.3). All 17 patients had a progression in the erosion score of the TSS. Only one patient had a progression also in the joint narrowing score of the TSS (2 U progression). Demographic and clinical variables were not associated with an increased risk of radiographic progression, except for NSAIDs use, which was more common in patients with radiographic progression (Table 1).

No patient without a PD signal at the baseline US examination experienced radiographic progression. Almost one-third of patients with a baseline PD signal in one or more joints had radiographic progression [17/59 (28.8%); RR 2.47 ($P < 0.0001$)]. PD grade 3 was associated with an RR of radiographic progression of 3.49 ($P < 0.05$) and PD grade 2 with an RR of 4.58 ($P < 0.01$) (Table 1). Patients with a total PD score $\geqslant 2$ had an RR of radiographic progression of 3.19 ($P < 0.0001$). Radiographic progression was observed in 16/44 (36.3%) patients with PD location 2 (RR 3.49, $P < 0.0001$), compared with only 1/15 (6.6%) with PD location 1 (RR 0.44, not significant) (Table 1). The joints with a PD signal at baseline were the site of radiographic progression in more than half of the cases [10/17 (56.9%)].

In the generalized linear model, the contributing variables were PD grade, number of joints with a PD signal,

TABLE 1 Baseline clinical and US variables of patients in stable DAS28 remission and association with radiographic progression

Variables	Total	Patients without radiographic progression	Patients with radiographic progression	Spearman's ρ	Risk ratio (95% CI)	*P*-value
Number	121	104	17			
Clinical variables						
Females, *n* (%)	105 (86.8)	90 (86.5)	15 (88.2)	–	0.87 (0.22, 3.51)	1.00
Age, mean (S.D.), years	56.0 (12.8)	62.0 (7.4)	55.0 (13.2)	0.18	– (−0.002, 0.34)	0.05
Disease duration, mean (S.D.), years	14.6 (8.9)	15.9 (10.0)	14.3 (8.7)	0.05	– (−0.13, 0.22)	0.60
Positive RF and/or ACPA, *n* (%)	86 (71.1)	71 (68.3)	15 (88.2)	–	1.29 (1.04, 1.61)	0.14
TSS at baseline, mean (S.D.)	91.2 (74.9)	119.1 (70.8)	86.7 (74.9)	0.18	– (0.00, 0.34)	0.05
TSS progression per year,[a] mean (S.D.)	8.7 (5.8)	11.9 (6.2)	8.2 (5.6)	0.16	– (−0.14, 0.33)	0.07
Number of DMARD treatments before biologics,[b] mean (S.D.)	2.4 (1.2)	2.3 (1.3)	2.4 (1.1)	−0.01	– (−0.20, 0.16)	0.88
NSAIDs use before biologics,[b] *n* (%)	82 (67.8)	69 (66.3)	13 (76.5)	–	1.15 (0.86, 1.55)	0.57
Cumulative prednisone dose before biologics,[b] mean (S.D.), g	27.8 (24.4)	34.1 (29.0)	26.8 (23.5)	0.12	– (−0.06, 0.29)	0.20
Prednisone daily dose before biologics,[b] mean (S.D.), mg	5.1 (1.9)	5.6 (1.1)	5.0 (2.0)	0.07	– (−0.11, 0.25)	0.48
DAS28 before biologics,[b] mean (S.D.)	5.0 (0.8)	5.3 (0.7)	5.0 (0.9)	0.16	– (−0.02, 0.33)	0.08
CRP before biologics,[b] mg/l, mean (S.D.), mg/l	18.8 (22.1)	17.5 (13.9)	19.0 (23.3)	0.03	– (−0.15, 0.21)	0.74
Number of biologic treatments, mean (S.D.)	1.4 (0.7)	1.6 (0.9)	1.4 (0.6)	−0.02	– (−0.20, 0.16)	0.85
Concomitant DMARDs, *n* (%)	72 (59.5)	59 (56.7)	13 (76.5)	–	1.34 (0.99, 1.84)	0.27
Concomitant NSAIDs, *n* (%)	24 (19.8)	17 (16.3)	7 (41.2)	–	1.25 (1.23, 5.15)	0.02
Prednisone daily dose, mean (S.D.), mg,	3.3 (2.1)	3.4 (2.2)	3.3 (2.1)	0.03	– (−0.14, 0.21)	0.71
US variables						
Number of joints with PD signal, *n* (%)						
1 joint	59 (48.8)	42 (40.4)	17 (100)	–	2.47 (1.96, 3.13)	<0.0001
2 joints	21 (17.3)	15 (14.4)	6 (35.3)	–	2.45 (1.10, 5.42)	<0.05
3 joints	7 (5.8)	5 (5.8)	2 (11.8)	–	2.45 (0.51, 11.62)	0.26
4 joints	3 (2.5)	2 (1.9)	1 (5.9)	–	3.05 (0.29, 31.92)	0.37
PD signal grade, *n* (%)						
Grade 1	34 (28.1)	27 (25.9)	7 (41.2)	–	1.58 (0.82, 3.05)	0.16
Grade 2	14 (11.6)	8 (7.7)	6 (35.3)	–	4.58 (1.82, 11.58)	<0.01
Grade 3	11 (9.1)	7 (6.7)	4 (23.5)	–	3.49 (1.14, 10.67)	<0.05
Total PD score $\geqslant$2, *n* (%)	35 (28.9)	23 (22.1)	12 (70.6)	–	3.19 (1.99, 5.13)	<0.0001
Power Doppler signal location						
Location 1, capsular or within synovial tissue without bone contact, *n* (%)	15 (12.4)	14 (13.5)	1 (5.9)	–	0.44 (0.06, 3.11)	0.91
Location 2, with bone contact or penetrating bone cortex, *n* (%)	44 (36.4)	28 (26.9)	16 (94.1)	–	3.49 (2.49, 4.90)	<0.0001

Association of clinical and US variables with radiographic progression are presented as correlations of continuous variables (*P*-values assessed by exact permutation distributions) and RRs of categorical variables (*P*-values assessed with two-tailed Fisher's exact test). [a]TSS at baseline divided by the number of years since RA onset. [b]Before the start of the first biologic treatment.

PD location, total PD grade (*F*-statistic *vs* constant model = 14.1, $P < 0.0001$, root mean square error = 0.48, adjusted $R^2 = 0.57$).

Discussion

Several US and MRI techniques and scores have been introduced to detect even subclinical disease activity [11]. US findings can predict radiographic progression in patients treated with conventional DMARDs [5, 6, 12]. This is the first study investigating the role of US findings in predicting radiographic progression in patients in remission induced by TNF-α blockers. In addition, it is the first study looking at the location of the PD signal.

In our study, synovial hypertrophy was found in all patients and almost half of the patients (48.7%) had a PD signal in one or more joints. These rates are higher when compared with other studies in RA patients in remission [3]. Indeed, our findings were consistent with the long disease duration of our patients, who also underwent several treatment changes before the current treatment.

In accordance with previous reports [2, 3], in our study the most involved joints were the small joints of the hand and, to a lesser extent, MTP joints. The tested joints are those considered in the radiographic scoring by the TSS. The choice of this set of joints was also supported by the evidence that the US assessment of wrists, MCP joints, MTP joints and ankles showed the highest sensitivity in detecting synovial hypertrophy and PD signal in patients in remission [13]. Notably, the US assessment of MTP joints does not seem to be pivotal, as they were never found as the sole site of US synovitis and did not identify patients who developed radiographic progression.

A small number of patients (14.1%) experienced radiographic progression, which was defined by a very sensitive cut-off ($\Delta TSS > 0$). All US findings were more significantly associated with radiographic progression compared with clinical characteristics and with baseline radiographic damage. Patients with a lower baseline TSS were even more prone to structural damage, with an almost significant association ($P = 0.05$). An explanation might be that both patients who progressed and those who did not showed high heterogeneity in disease duration. Nevertheless, synovial inflammation detected by US was more suggestive of structural damage compared with baseline erosivity expressed by the TSS.

A PD signal in one or more joints at baseline increased by 2-fold the risk of radiographic progression at the 1 year follow-up. Patients with higher PD grades more frequently experienced radiographic progression. A total PD score $\geqslant 2$ was significantly associated with a 3-fold increased risk of radiographic progression. This cut-off might be suitable for use in clinical practice. A total PD score $\geqslant 2$ could either be a PD signal with grade $\geqslant 1$ in two joints or a PD grade $\geqslant 2$ in a single joint.

PD location was found to be a strong predictor of radiographic progression. A PD signal in contact with the bone or penetrating into the bone surface (location 2) was associated with a 3-fold increased risk of radiographic progression. This result supports the pathogenic role of synovial inflammation in the erosive damage of the adjacent bone surface. Multivariate regression analysis showed that a PD signal in one or more joints and PD grade were more significantly associated with progression of the TSS rather than PD location. Nevertheless, PD location might be a useful US score in clinical practice. PD location is simple to classify and interreader agreement was high in our study. As soon as a PD signal in location 2 is found in any joint, the patient can be identified as at risk of structural progression and treatment can be changed accordingly.

Notably, in almost half of the cases we observed radiographic progression in a different joint compared with the site of a positive PD signal at baseline. This finding is consistent with a previous study by Brown *et al.* [6]. The limited sensitivity of radiographs in detecting structural damage and of US in detecting osteitis might partly explain this disconnect between synovitis and erosion. A disconnect hypothesis between synovitis and erosion development in RA joints, called the two-compartment model, has also been suggested. In patients treated with a combination of DMARDs and TNF-α blockers, progression of bone erosion can be absent despite incomplete suppression of synovitis as detected by MRI or US [14]. Thus the absence of radiographic progression does not seem to be related to the complete suppression of imaging-detected synovitis [2]. TNF-α blockers directly inhibit the osteoclast-mediated bone destruction pathway [7] and might be more effective in halting erosive damage rather than suppressing synovitis. Osteitis, which precedes bone erosion, and synovitis might be controlled by interfering with different pathogenic pathways.

US examination with a PD signal is useful in evaluating patients in clinical remission by identifying those who are at high risk of radiographic damage despite treatment with TNF-α blockers. Specifically, patients with higher PD grades and those with a PD signal in contact with or penetrating bone are more prone to radiographic progression. Further studies are needed to confirm the usefulness of variables such as total PD score $\geqslant 2$ and PD location 2. If these US variables prove to be reliable, US examination might be limited to a few joints in order to identify patients who might benefit from more aggressive treatment.

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