**GRADE AND LOCATION OF POWER DOPPLER ARE PREDICTIVE OF RADIOGRAPHIC DAMAGE PROGRESSION IN RHEUMATOID ARTHRITIS PATIENTS IN CLINICAL REMISSION INDUCED BY TNFα BLOCKERS**

Bernd Raffeiner1,2, Enrico Grisan3, Francesca Ometto1, Costantino Botsios1, Roberto Stramare4, Gaia Rizzo3, Livio Bernardi1, Leonardo Punzi1, Andrea Doria1.

1. Rheumatology Unit, Department of Medicine - DIMED, University of Padova, Padova, Italy

2. Rheumatology Unit, Department of Medicine, Central Hospital of Bolzano, Bolzano, Italy

3. Department of Information Engineering, University of Padova, Padova, Italy

4. Radiology, Department of Medicine – DIMED, University of Padova, Padova, Italy

**AUTHORS’ CONTRIBUTION**

BR made substantial contribution to study conception and design, to data acquisition, analysis and interpretation and drafted the manuscript. EG and GR were involved in analysis and interpretation of data. FO made substantial contribution to data analysis and interpretation and drafted the manuscript. CB, RS and LB were involved in the study conception and design and in data acquisition. LP and AD made substantial contribution to study conception and design and to revise the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

**CORRESPONDING AUTHOR**

MD, PhD, Bernd Raffeiner

Rheumatology Unit, Department of Medicine – DIMED, University of Padova

Rheumatology Unit, Department of Medicine, Central Hospital of Bolzano, Bolzano, Italy

Via Giustiniani, 2, 35128 Padova (Italy)

Phone: +39 049 821 21 90

Fax: +39 049 821 21 91

berndraffeiner@yahoo.com

**SHORT TITLE**

Doppler Predicts Radiographic Progression

**ABSTRACT**

**Objectives**

To investigate the association of power Doppler (PD) signal, grade and location with radiographic progression in rheumatoid arthritis (RA) patients in remission.

**Methods**

A prospective observational study was conducted on consecutive 125 RA patients in stable DAS28 remission (≥6 months) achieved with anti-TNFα. At baseline, patients in stable remission underwent radiographic and ultrasound examination of wrists, metacarpophalangeal, proximal interphalangeal, and metatarsophalangeal joints.

Semi-quantitative PD scoring (0-3) was recorded. We scored PD according to two locations: 1) capsular or within synovia without bone contact, and 2) with bone contact or penetrating bone cortex.

Radiographic progression was defined as a change in van der Hejide modified-total Sharp Score (∆TSS)>0 at 1-year follow-up.

Risk ratios (RR) 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 PD signal at least in one joint: 57.6% (34/59) had a maximum PD grade of 1, 23.7% (14/59) 2 and 18.6% (11/59) 3. PD location 2 was found in 74.6% patients (44/59). At 1-year follow-up, 17/121 patients experienced radiographic progression: all had a positive PD signal at baseline (RR 2.47, p<0.0001).

Baseline PD grade 2 and grade 3 were associated with a RR of radiographic progression of 4.58, p <0.01 and 3.49 p <0.05, respectively, and PD location 2 with a RR of 3.49, p <0.0001.

**Conclusions**

Higher PD grades and PD in contact with/or penetrating bone profile 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-TNFα agents.

**Introduction**

The predictive value of ultrasound (US) findings in rheumatoid arthritis (RA) has gained an increasing interest in recent years especially with regard to the assessment of patients in remission [1]. US synovitis already proved to be predictive of radiographic progression in patients treated with conventional DMARDs [2], but no information is available in patients treated with TNFα blockers. In patients treated with DMARDs, significant correlation was found between US findings and DAS28 change at 1-year follow-up or radiographic progression, while no association was found with baseline, clinical, laboratory and functional variables [3]. The Leeds group has reported that joint inflammation detected by US or magnetic resonance imaging (MRI) is frequent even in patients in clinical remission [4,5]. In RA patients achieving clinical remission with the combination of DMARDs and a TNFα blockers, US gray scale synovitis was detected in 50.7% of the examined joints and power Doppler (PD) synovitis in 15.2% [6]. Imaging synovitis was most frequently observed in wrists, hands and feet, while PD signal was uncommon in the metatarsophalangeal joints (MTPs), except in the fifth MTP joint [6].

In RA patients treated with DMARDs, baseline US synovial hypertrophy, PD and MRI synovitis scores in individual joints were significantly associated with progressive radiographic damage in the same joint [7]. A significant association was also found between PD score at baseline and structural progression over 12 months in asymptomatic metacarpophalangeal joints (MCPs); in addition, a 12 fold higher odds of structural progression was observed in the joints with increased PD signal [7].

TNFα blockers are known to be highly effective in blocking radiological damage through direct inhibition of osteoclastogenesis [8,9] and proved effective even at a half dose in halting radiological damage if remission is stable [10]. The association of PD with damage progression in RA patients in remission achieved with TNFα blockers has not been unraveled yet.

The aim of our study was to investigate the rate of US synovitis, defined as synovial hypertrophy and PD signal, in patients in clinical remission (DAS28<2.6) induced by TNFα blockers and to assess the grade and location of PD signal. Further, the association of PD signal, PD grade and PD location with radiographic progression was investigated.

**Methods**

A prospective observational study was performed in 125 consecutive RA patients on TNFα blockers, who were in stable (≥6 months) DAS28 remission [11]. The study was approved by the local Ethics Committee and all patients signed an informed consent.

At baseline, demographics, clinical and laboratory variables and treatment information of patients in stable DAS28 remission were collected. US examination was performed in dorsal view of MCPs, proximal interphalangeal joints (PIPs), wrists (inter- and radio-carpal) and MTPs with Logiq 7 (GE, [Fairfield, Connecticut](https://it.wikipedia.org/wiki/Fairfield_(Connecticut))) and 18 MHz linear probe.

Active synovitis was identified by PD and the number of joints with positive PD signal was recorded together with the semi-quantitative PD scoring, ranging from 0 to 3. PD grade of each patient was defined according to the highest PD grade found in the assessed joints. The location of PD signal in the synovial tissue was scored as follows: capsular or within synovia without bone contact (location 1) and with bone contact or penetrating bone cortex (location 2) (Figure 1). PD location in each patient was defined as location 2 if location 2 was found at least in one joint; otherwise PD location was defined as location 1.

All patients underwent hands and feet radiographs at baseline and at 1-year follow-up. Radiographic progression was defined as a change in van der Hejide modified-total Sharp Score (∆TSS)>0.

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 [12] assessed using two-tailed Fisher's exact test [13,14]. Statistical analysis was performed using Matlab 2014b (The Mathworks, Inc.).

**Results**

One hundred twenty-one out of 125 patients had a complete baseline assessment and 1-year radiographic follow-up and were included in the analysis. Baseline characteristics of patients and treatments are reported in Table 1.

At the baseline US evaluation, all patients had synovial hypertrophy at least in one joint and almost half of the patients (47.8%, 59/12) had positive PD at least in one joint. PD signal was observed in one joint in 64.4% of the patients (38/59) and in ≥ 2 joints in 35.6% (22/59). The maximum number of joints with positive PD signal at baseline was 8. Among the 4114 analyzed joints (10 MCPs, 10 PIPs, 4 wrists and 10 MTPs per patient), 94 (2.3%) had positive PD: 92.4% (87/94) in the hands, 63.8% (60/94) in the wrists, 21.2% (20/94) in MCPs, 7.5% (7/94) in PIPs, and 7.5% (7/94) in MTPs.

Maximum PD grade was 1 in 34/59 (57.6%) patients, 2 in 14/59 (23.7%), and 3 in 11/59 (18.6%). The majority of PD signals (44/59, 74.6%) was in location 2, with bone contact or penetrating bone cortex.

Only 17/121 (14.0%) patients experienced radiographic progression after one year, defined as a ∆TSS>0. Mean ∆TTS in the 17 patients who progressed was 1.14 ± 1.63. Demographics, clinical, laboratory variables and treatments were not associated with an increased risk of radiographic progression (Table 1).

No patient without PD signal at the baseline US examination experienced radiographic progression, while almost one third of the patients with baseline PD signal in at least one joint had radiographic progression (17/59, 28.8%): the RR of radiographic progression in patients with baseline positive PD signal in at least one joint was 2.47, p <0.0001 (Table 2).

Four out of 11 (36.6%) patients with PD grade 3 had radiographic progression (RR 3.49, p<0.05), 6/14 (42.8%) with grade 2 (RR 4.58, p<0.01) and 7/34 (20.6%) with grade 1 (RR 1.58, not significant) (Table 2).

Sixteen out of 44 (36.3%) patients with PD location 2 had radiographic progression (RR 3.49, p <0.0001), compared with only 1/15 (6.6%) with PD location 1 (RR 0.44, not significant) (Table 2).

The joints with PD signal at baseline were the site of radiographic progression in half of the cases 10/17 (56.9%), while in the other 43.1% of patients the site of radiographic progression was different.

**Discussion**

In the last years, several US and MRI scores and techniques have been introduced to monitor RA in remission and detect even subclinical disease activity [15].

Several studies have shown the ability of US to detect gray scale synovitis and synovial PD activity in a high percentage of RA patients in clinical remission treated with conventional DMARDs [16]. The US assessment of wrists, MCPs, ankles, and MTPs showed the highest sensitivity in detecting synovial hypertrophy and PD signal in patients in remission according to DAS28 and SDAI [17]. In our study we tested PD signal in MCPs, PIPs, wrists and MTPs since these are the joints considered in the radiographic scoring by TSS.

Synovial hypertrophy was found in all patients in clinical remission and this finding was consistent with the long disease duration of our patients. About half of the patients (48.7%) had PD signal in at least one joint, despite sustained DAS28 remission induced by TNFα blockers. In our study the most involved joints were the small joints of the hand and, to a lesser extent, MTPs as previously reported [5]. The US assessment of MTPs does not seem to be mandatory, as it was never found as the sole site of US synovitis. If we had excluded the US assessment of MTPs at baseline, we would not have missed any patients who developed radiographic progression afterwards.

Subclinical synovitis detected with PD signal has already proved predictive of disease relapse [18-20] and of radiographic progression [7,21]. Disease relapses in RA are associated with radiographic progression [22] and PD signal proved to be the most accurate predictor of disease relapse. Positive PD has been associated with worse clinical and functional outcomes at 6 and 12 months in RA patients in remission treated with conventional DMARDs and has proved to predict the failure of biologic tapering in RA patients in remission [23-25]. In the study by Foltz et al., 30.6% of patients in remission had a disease relapse and 10.6% radiographic progression over 1-year follow-up [21]. The baseline number of PD positive joints was also a predictor of relapse (OR 6.3) and the baseline grade of PD synovitis predicted disease progression (OR 1.4), whereas MRI was not predictive of adverse clinical and radiographic outcomes [21].

In our patients no disease relapses were observed probably because of the stringent definition of clinical remission. Indeed, we considered only patients who maintained remission for at least 6 months, whereas in the study by Foltz et al. both patients in remission or in low disease activity for at least 2 months were included. Further, all patients in our study were treated with TNFα blockers compared with 20% in the study by Foltz et al.

We observed subclinical disease activity even in patients in DAS28 remission induced by TNFα blockers. Notably, PD signal at least in one joint at the baseline increased by 2-fold the risk of radiographic progression. We also confirmed that patients with higher PD grades were more prone to experience radiographic progression.

Remarkably, we were able to identify the location of PD signal as a strong predictor of radiographic progression. If PD signal is in contact with the bone or penetrates into the bone surface (location 2), the risk of radiographic progression is increased by more than 3-fold, whereas a PD signal location 1 seems to be associated with a lower risk of structural damage. This is the first study specifically investigating the location of the PD signal and our results support the pathogenic role of synovial inflammation in the erosive bone damage. Brown et al. found that synovitis, detected by MRI or US, is predictive of structural damage and reported that PDUS synovitis positively predicted erosive radiographic progression either in the single patient or in the single joint [7].

Besides, a “disconnect” hypothesis between synovitis and erosion development in RA joints has been suggested: progression of bone erosion can be absent despite persistent MRI and US synovitis in patients treated with the combination of DMARDs and TNFα blockers [26]. Thus, the absence of radiographic progression in patients treated with the combination of DMARDs and TNFα blockers does not seem to be related to the complete suppression of imaging-detected synovitis [5]. The combination of conventional DMARDs with TNFα blockers might be more effective in halting erosive bone damage than suppressing synovitis. The “disconnect” hypothesis, also called “two-compartment model”, might explain why in our study the sites of baseline PD signal were not the sites of radiographic progression in almost half (43.1%) of the cases.

The limited sensitivity of X-rays in detecting structural damage and of US in detecting osteitis might explain part of the disconnection between synovitis and erosion. However, there is clear evidence that osteitis is strongly predictive of bone erosion even more than synovitis, supporting the idea that there is a direct association of bone damage with early signs of bone inflammation rather than with synovial inflammation. The “disconnect” hypothesis further supports the role of TNFα blockers in halting osteoclast-mediated bone destruction pathway. Notably, TNFα blockers inhibit the erosive pathway, even if osteitis and synovitis show a low-grade progression.

PD proved to be useful in evaluating patients in clinical remission by identifying those who are at high risk of radiographic damage despite treatment with TNFα blockers. Specifically, patients with higher PD grades and those with PD signal in contact or penetrating bone profile at least in one joint are more prone to radiographic progression.

**KEY MESSAGES**

1. Almost half of rheumatoid arthritis patients in DAS28 remission have positive power Doppler signal.
2. Higher power Doppler grades are associated with radiographic progression.
3. Power Doppler signal in contact with/or penetrating bone profile is associated with radiographic progression.

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None.

**CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest.

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No funding was required.

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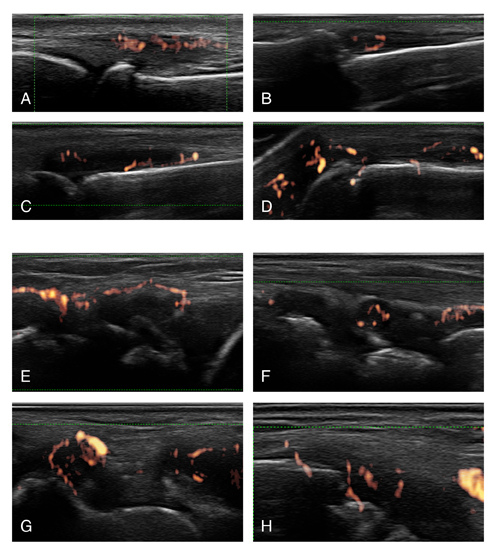
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**Table 1**. **Baseline clinical and ultrasound variables of patients in stable DAS28 remission and association with radiographic progression.**

Association of clinical and ultrasound variables with radiographic progression are presented as correlations of continuous variables (p-values assessed by exact permutation distributions), and risk ratios of categorical variables (p-value assessed with two-tailed Fisher's exact test).

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

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**Figure 1. Classification of power Doppler location.** Location at the metacarpophalangeal level A-D) and at the wrist level (E-H). Location 1: capsular (A,E) or within synovia (B,F) without bone contact; location 2: with bone contact (C,G) or penetrating bone cortex (D,H). power Doppler location of each patient was defined as location 2 if location 2 was found at least in one joint, otherwise power Doppler location was defined as location 1.