Original article

Ultrasonographic examination of rheumatoid arthritis patients who are free of physical synovitis: power Doppler subclinical synovitis is associated with bone erosion

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Abstract

Objective. The aim of this study was to investigate the characteristics of power Doppler (PD) subclinical synovitis in patients with RA who achieve clinical remission free from physical synovitis.

Methods. Twenty-nine RA patients were consecutively enrolled. All of the patients had achieved clinical remission [simplified disease activity index (SDAI) 3.3] for at least 6 months at the musculoskeletal ultrasound (MSKUS) examination. Additionally, none of the patients exhibited tender joints at 68 sites or swollen joints at 66 sites. MSKUS of bilateral wrist and finger joints, including the first to fifth MCP joints, the first IP joint and the second to fifth PIP joints, was performed and the findings obtained by grey scale (GS) and PD were graded on a semi-quantitative scale from 0 to 3.

Results. The median disease duration upon the introduction of DMARDs was 3 months and that at MSKUS examination was 21 months. The percentages of patients with PD synovitis in at least one joint were PD grade 1, 58.6%; PD grade 2, 31.0% and PD grade 3, 6.9%. The use of biological agents was low in patients with PD synovitis grade 2 (P < 0.05). The presence of US bone erosion was high by patient (P < 0.05) and by joint (P < 0.0001) with PD synovitis as compared with those without PD synovitis. However, no correlations were found between PD synovitis measures and serum biomarkers, including angiogenesis factors.

Conclusion. PD subclinical synovitis correlates with several clinical characteristics, whereas conventional serum biomarkers are not useful for indicating the presence of subclinical PD synovitis.

Key words: rheumatoid arthritis (RA), musculoskeletal ultrasonography (MSKUS), remission, synovitis, bone erosion.

Introduction

Recently the outcome for patients with RA has improved due to improvements in therapy, and clinical remission is now a realistic therapeutic goal [1]. There are several definitions of clinical remission based on various composite scores, such as the DAS, 28-joint DAS (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and a Boolean definition as recently proposed by the ACR or European League Against Rheumatism (EULAR) [2]. The latter three criteria based on SDAI, CDAI and the Boolean definition are more stringent than those based on DAS28 [2]. The RA patients achieving remission according to the SDAI, CDAI or Boolean definition have a greater chance of structural remission than the patients achieving DAS28 remission; however, some reports have pointed out the presence...
of radiographic progression despite the achievement of these types of clinical remission [3–5], which reflects the inadequate sensitivity of the conventional approaches in detecting synovitis.

In this regard, musculoskeletal ultrasound (MSKUS) is an ideal modality to detect subclinical joint inflammation that may lead to further radiographic progression since MSKUS is more sensitive than physical examination for detecting joint injury in patients with RA [6–8]. Various kinds of joint injury, including articular synovitis, tenosynovitis and bone erosion, can be recorded by grey scale (GS) and power Doppler (PD) techniques [9, 10]. We recently reported that the presence of PD synovitis grade ≥ 2 is a very RA-specific MSKUS finding among patients with early arthritis [11]. As stated in previous reports, including those by us as well as other investigators, PD synovitis has been suggested to reflect the pathologic alterations of rheumatoid synovial inflammation in patients with RA better than GS synovitis [8, 12–14]. The qualitative importance of subclinical synovitis, as first described by Brown et al. [8], is that the joints with PD signals may develop continued structural deterioration irrespective of the achievement of good clinical status in established RA patients with a median disease duration of 7 years.

Recently, more detailed information regarding PD synovitis in RA patients with good clinical status has been accumulated [8, 14–16]. Saleem et al. [15] found that PD synovitis remains in long-standing established RA patients achieving clinical remission evaluated by the SDAI or Boolean definition. They also showed that those patients in whom PD synovitis remains will develop clinical flare-ups during treatment with conventional DMARDs [16]. Residual PD synovitis is also predictive of clinical flare-ups in early stage RA patients with a mean disease duration of 3.8 months treated by conventional DMARDs [14]. These data strongly suggest that RA patients in clinical remission with residual PD synovitis do not achieve ‘true’ remission and are at risk for subsequent structural deterioration and flares. However, the subjects in the above studies exhibited slightly tender or swollen joints upon physical examination even if they had achieved clinical remission [8, 14–19]. Therefore it appears to be desirable to select RA patients who have achieved sustained clinical remission without any tender or swollen joints in order to examine the characteristics of ‘real’ subclinical PD synovitis in individuals who are almost completely free from synovitis by physical examination. We have serially selected these kinds of patients and tried to characterize the residual subclinical PD synovitis in association with biomarkers.

Materials and methods

Patients

Twenty-nine RA patients who fulfilled the 2010 RA classification criteria [20] were consecutively recruited in the present study. All of the patients achieved clinical remission (SDAI 3.3) for at least 6 months upon MSKUS examination. Furthermore, all of the patients exhibited no tender joints among 68 sites and no swollen joints among 66 sites upon MSKUS examination. They were recruited from the Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University from July 2011 through February 2012. Patients gave their informed consent and the study was approved by the Institutional Review Board of Nagasaki University. Serum samples were collected and stored at −20°C upon MSKUS examination until the assay.

Clinical and laboratory assessment

Clinical evaluation was performed by Japan College of Rheumatology (JCR)-certified rheumatologists (H.N. and A.K.) who were blinded to the MSKUS findings. Agreement for the presence of tender joints and swollen joints by physical examination between the two rheumatologists were very high: the kappa coefficient of distribution of tender joints was 0.92 and that of swollen joints was also 0.92 in both wrist and finger joints of five other active RA patients. Disease activity was evaluated by the DAS28-ESR, SDAI, CDAI and Boolean remission. In using DAS28-ESR, we followed the criteria set by the EULAR, and in using CDAI and SDAI we followed the method recommended by Smolen et al. [21]. Boolean remission is defined by all of the following parameters: tender joint count (TJC) ≤ 1, swollen joint count (SJC) ≤ 1, patient global assessment (PtGA) ≤ 1 cm and CRP ≤ 1 mg/dl [22].

The following laboratory variables were assessed: RF (Dade Behring, Marburg, Germany; cut-off value 14 IU/ml), ACPA (DIASTAT anti-CCP, Axis-Shield, Dundee, UK; cut-off value 4.5 U/ml), CRP (Eiken Chemical, Tokyo, Japan), ESR, MMP-3 (Daichi Pure Chemicals, Fukuoka, Japan), vascular endothelial growth factor (VEGF) (Quantikine, R&D Systems, Abingdon, UK), angiopoietin-2 (Quantikine, R&D Systems) and soluble receptor activator of nuclear factor κB ligand (sRANKL) (Biomedica, Wien, Austria). Clinical disease activity as well as serum variables were evaluated on the day of the MSKUS examination.

MSKUS assessment

Each patient underwent an MSKUS assessment on the same day as the clinical evaluation by a JCR-certified rheumatologist (S.K.) who was blinded to the clinical findings (S.K. is also an instructor of MSKUS certified by the JCR with 7 years experience in MSKUS). Images from all the examinations were stored and the US scoring reliability was examined in randomly selected patients at the end of the study. A systematic multiplanar GS and PD examination of 22 joints was performed with the same scanner (Toshiba AplioXG) using a multifrequency linear transducer (12 MHz). The US score included the following 22 joints: bilateral wrists (intracarpal, radiocarpal and ulnocarpal recesses) and finger joints including the first to fifth MCP joints, the first IP joint and the second to fifth PIP joints (dorsal recess). All joint regions were sonographically examined in a standardized manner according to the EULAR [9] and JCR guidelines. These are the same
Residual subclinical synovitis on MSKUS in 29 RA patients achieved definitive clinical remission

The numbers (percentages) of patients with subclinical synovitis present in at least one joint were GS grade 1, 21 (72.4%); GS grade 2, 10 (34.5%); GS grade 3, 3 (10.3%); PD grade 1, 17 (58.6%); PD grade 2, 9 (31.0%) and PD grade 3, 2 (6.9%). The median (range) GS and PD scores were 2 (0–15) and 1 (0–12), respectively.

Comparison of clinical characteristics between patients with subclinical PD synovitis and patients without PD synovitis

The clinical characteristics were compared between patients with subclinical PD synovitis and patients without PD synovitis, and between patients with PD grade 2 and patients with PD grade 1 or 0 (Table 1). Age, gender, disease duration upon the introduction of DMARDs, disease duration at MSKUS examination, remission duration, the prevalence of ACPA and RF, the use of conventional DMARDs and disease activity were not different among the groups. In addition, parameters evaluating clinical disease activity at the MSKUS examination were comparably very low in each group (middle part of Table 1). However, in the patients with PD grade 2 as compared with patients without, the use of biologic agents was significantly lower (P = 0.032). The same tendency was also observed in patients with and patients without PD synovitis (P = 0.12). In addition, the PtGA was 0 in 10 patients, whereas it was > 0 in the remaining 19 patients. The percentage of patients having PD synovitis (70% in patients with PtGA = 0, whereas 53% in patients with PtGA > 0) and total PD score (mean score 2 in patients with PtGA = 0, whereas 1 in patients with PtGA > 0) were not different in either the 10 patients or 19 patients.

Comparison of MSKUS findings between patients with subclinical PD synovitis and patients without PD synovitis

The MSKUS findings were also compared between patients with subclinical PD synovitis and patients without PD synovitis, and between patients with PD grade 2 and patients with PD grade 1 or 0 (Table 1). As suspected, the total PD score was significantly higher in the patients with PD synovitis (P < 0.0001) and the patients with PD grade 2 (P = 0.0001). Additionally, the total GS score was significantly higher in the patients with PD synovitis (P < 0.0001) and the patients with PD grade 2 (P = 0.001). Furthermore, the percentage of patients with MSKUS bone erosion was significantly higher in the patients with PD synovitis (P = 0.032) and the patients with PD grade 2 (P = 0.0007). We confirmed the association of PD synovitis and US bone erosion by analysing their coexistence in a total of 638 joints from 29 patients. As shown in Table 2, there was a marked association between PD synovitis and MSKUS bone erosion (P < 0.0001).
<table>
<thead>
<tr>
<th></th>
<th>PD negative (n = 12)</th>
<th>PD positive (n = 17)</th>
<th>P-value</th>
<th>PD grade 0/1 (n = 20)</th>
<th>PD grade 2/3 (n = 9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), yearsa</td>
<td>50.5 (30-72)</td>
<td>57.0 (35-80)</td>
<td>0.36</td>
<td>59.5 (30-80)</td>
<td>56 (35-74)</td>
<td>0.49</td>
</tr>
<tr>
<td>Gender, female/male</td>
<td>9/3</td>
<td>13/4</td>
<td>0.70</td>
<td>15/5</td>
<td>7/2</td>
<td>0.63</td>
</tr>
<tr>
<td>Disease duration at the introduction of DMARDs, median (range), monthsa</td>
<td>3 (1-36)</td>
<td>3 (1-36)</td>
<td>0.95</td>
<td>3 (1-36)</td>
<td>2 (2-6)</td>
<td>0.85</td>
</tr>
<tr>
<td>Disease duration at MSKUS examination, median (range) monthsa</td>
<td>20 (12-67)</td>
<td>21 (11-300)</td>
<td>0.64</td>
<td>20 (11-67)</td>
<td>21 (11-300)</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration of remission, median (range), monthsa</td>
<td>11 (6-24)</td>
<td>10 (6-26)</td>
<td>0.95</td>
<td>9.5 (6-26)</td>
<td>12 (6-21)</td>
<td>0.48</td>
</tr>
<tr>
<td>Positivity of ACPA, n (%)</td>
<td>10 (83.3)</td>
<td>15 (88.2)</td>
<td>0.56</td>
<td>16 (80.0)</td>
<td>9 (100)</td>
<td>0.20</td>
</tr>
<tr>
<td>Positivity of RF, n (%)</td>
<td>10 (83.3)</td>
<td>16 (94.1)</td>
<td>0.75</td>
<td>18 (90.0)</td>
<td>8 (88.9)</td>
<td>0.78</td>
</tr>
<tr>
<td>Conventional DMARDs therapy, n (%)</td>
<td>7 (58.3)</td>
<td>5 (29.4)</td>
<td>0.12</td>
<td>11 (55.0)</td>
<td>1 (11.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Concomitant steroid, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>—</td>
</tr>
<tr>
<td>TJC, n/68</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>SJC, n/66</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>PPGA, median (range), mmn</td>
<td>3 (0-10)</td>
<td>3 (0-10)</td>
<td>0.38</td>
<td>3 (0-10)</td>
<td>0 (0-10)</td>
<td>0.13</td>
</tr>
<tr>
<td>EGA, median (range), mmn</td>
<td>3 (0-8)</td>
<td>3 (0-10)</td>
<td>0.54</td>
<td>3 (0-10)</td>
<td>1 (0-10)</td>
<td>0.27</td>
</tr>
<tr>
<td>CRP, median (range), mg/dln</td>
<td>0.03 (0.01-0.34)</td>
<td>0.05 (0.02-0.22)</td>
<td>0.09</td>
<td>0.03 (0.01-0.34)</td>
<td>0.05 (0.02-0.22)</td>
<td>0.07</td>
</tr>
<tr>
<td>ESR, median (range), mm/hn</td>
<td>9 (2-25)</td>
<td>11 (4-20)</td>
<td>0.13</td>
<td>10.5 (2-25)</td>
<td>8 (4-14)</td>
<td>0.10</td>
</tr>
<tr>
<td>DAS28-ESR, median (range)a</td>
<td>1.60 (0.53-2.30)</td>
<td>1.74 (0.97-2.17)</td>
<td>0.17</td>
<td>1.73 (0.53-2.30)</td>
<td>1.60 (0.97-1.90)</td>
<td>0.09</td>
</tr>
<tr>
<td>CDAI, median (range)a</td>
<td>0.65 (0-1.80)</td>
<td>0.60 (0-2.00)</td>
<td>0.48</td>
<td>0.60 (0-1.80)</td>
<td>0.10 (0-2.00)</td>
<td>0.25</td>
</tr>
<tr>
<td>SDAI, median (range)a</td>
<td>0.77 (0.01-2.01)</td>
<td>0.62 (0.02-2.03)</td>
<td>0.81</td>
<td>0.75 (0.01-2.01)</td>
<td>0.24 (0.02-2.03)</td>
<td>0.45</td>
</tr>
<tr>
<td>Boolean remission, n (%)</td>
<td>12 (100)</td>
<td>17 (100)</td>
<td>—</td>
<td>20 (100)</td>
<td>9 (100)</td>
<td>—</td>
</tr>
<tr>
<td>MSKUS findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total GS score, median (range)a</td>
<td>0 (0-2)</td>
<td>4 (1-15)</td>
<td>&lt;0.0001</td>
<td>1 (0-11)</td>
<td>4 (2-15)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total PD score, median (range)a</td>
<td>0</td>
<td>2 (1-12)</td>
<td>&lt;0.0001</td>
<td>0 (0-4)</td>
<td>3 (2-12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Tenosynovitis, n (%)</td>
<td>2 (16.7)</td>
<td>4 (23.5)</td>
<td>0.51</td>
<td>3 (15.0)</td>
<td>3 (33.3)</td>
<td>0.53</td>
</tr>
<tr>
<td>Bone erosion, n (%)</td>
<td>1 (8.3)</td>
<td>8 (47.1)</td>
<td>0.03</td>
<td>2 (10.0)</td>
<td>7 (77.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aWithin-group comparisons were assessed with the Mann-Whitney U test and $\chi^2$ test. EGA: evaluator global assessment.
Comparison of serum biomarkers between patients with subclinical PD synovitis and patients without PD synovitis

Table 3 summarizes the data. Serum concentrations of MMP-3, VEGF, angiopoietin-2 and sRANKL in the present 29 patients were comparable with those in normal subjects. In addition, there were no differences in these biomarkers regardless of the presence of PD synovitis or PD grade ≥2. Furthermore, no correlation was observed between total PD score and any of the biomarkers (Fig. 1). Since some characteristics distributed in the patients with PD synovitis or PD grade ≥2 were determined, we tried to confirm the contributions of these characteristics by logistic regression analysis (SAS, version 9.2; SAS Institute, Cary, NC, USA). However, we were unable to obtain definitive results, probably due to the small sample size (data not shown).

Discussion

Subclinical synovitis is defined as joint inflammation determined not by physical examination, but by MSKUS or MRI [6-8, 14-17, 26]. The importance of subclinical synovitis, especially as determined by power Doppler US, has been strengthened by several reports showing that its presence is predictive of further radiographic progression [14, 27] or clinical flare-ups [14, 27]. To more strictly assess the role of subclinical PD synovitis in patients with RA, none of the patients in the present study exhibited tender or swollen joints upon physical examination, indicating that our data represent the real nature of subclinical PD synovitis as well as patients who have achieved definitive clinical remission with subclinical PD synovitis. To our knowledge, this is the first examination of patients with early stage RA involved in ‘true’ subclinical PD synovitis.

A few reports have explored the characteristics of PD synovitis in Caucasian early stage RA patients who have achieved clinical remission [14, 28]. Although clinical disease activity was lower in the present study compared with these reports, some of the patients in previous reports exhibited tender or swollen joints, the percentage of patients with PD synovitis was higher in the present study than in the previous reports [14, 28]. The positivity rates of ACPA (29% in Scirè et al. [14] and RF (39%) in Scirè et al. [14] and 41% in Sakellariou et al. [28]) in the present cases were much higher than in the previous cases, which may have influenced the results. Alternatively, Japanese RA patients might be more susceptible to joint inflammation as compared with Caucasian RA patients. However, these points need to be clarified in future studies.

In addition, we revealed the characteristics of early stage RA patients with subclinical PD synovitis. With regard to therapies, the absence of PD synovitis was likely to be associated with biologic agents. There is increasing evidence that biologic agents are superior to conventional DMARDs in terms of radiographic progression [1, 29, 30]. Since the existence of PD signals is a risk factor for further radiographic progression in patients with RA [8, 27], the suppression of PD signals by biologic agents may explain the preferential protective effect toward joint damage as compared with conventional DMARDs. Furthermore, the percentage of patients with US bone erosion was higher in those with subclinical PD synovitis than in those without PD synovitis. Additionally, the frequency of the joints with US bone erosion was much higher in the joints with PD signals as compared with the joints without PD signals. These data indicate that the coexistence of PD signals with US bone erosion is a characteristic feature of US images in patients with early stage RA even after they have achieved definitive clinical remission. It would be reasonable for patients with PD synovitis to show a high GS score, since

### Table 2

Comparison between PD-positive synovitis and MSKUS bone erosion

<table>
<thead>
<tr>
<th>Bone erosion</th>
<th>PD negative</th>
<th>PD positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>600</td>
<td>21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>positive</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Within-group comparisons were assessed with the χ² test.

### Table 3

Comparison of serum biomarkers between patients with and patients without PD-positive synovitis

<table>
<thead>
<tr>
<th>Serum biomarker</th>
<th>PD negative (n=12)</th>
<th>PD positive (n=17)</th>
<th>P-value</th>
<th>PD grade 0/1 (n=20)</th>
<th>PD grade 2/3 (n=8)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP-3, median (range), ng/ml</td>
<td>50.7 (35.1–69.6)</td>
<td>53.0 (31.8–102)</td>
<td>0.79</td>
<td>53.8 (35.1–69.6)</td>
<td>50 (31.8–102)</td>
<td>0.35</td>
</tr>
<tr>
<td>VEGF, median (range), pg/ml</td>
<td>268 (56.9–540)</td>
<td>271 (0–721)</td>
<td>0.45</td>
<td>270 (0–721)</td>
<td>257 (147–664)</td>
<td>0.91</td>
</tr>
<tr>
<td>Angiopoietin-2, median (range), pg/ml</td>
<td>1954 (885–4429)</td>
<td>1895 (1449–3335)</td>
<td>0.80</td>
<td>2085 (885–4429)</td>
<td>1803 (1449–2543)</td>
<td>0.08</td>
</tr>
<tr>
<td>Ampli-sRANKL, median (range), pmol/l</td>
<td>0.4 (0.0–0.290)</td>
<td>0 (0–0.478)</td>
<td>0.90</td>
<td>0 (0–0.478)</td>
<td>0 (0–0.425)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Serum levels [median (range)] of healthy controls (n=10): VEGF: 291 (32–602) pg/ml; angiopoietin-2: 1827 (1230–2587) pg/ml; ampli-sRANKL: 0.009 (0–0.308) pmol/l. Within-group comparisons were assessed with the Mann-Whitney U test.
the severity of the PD score usually correlates with that of the GS score in patients with RA. Considering that the presence of PD signals predicts further radiographic progression [8, 27], subclinical PD synovitis is thought to be pathologically still active and is thus supposed to coexist with US bone erosion, possibly leading to further joint damage. However, longitudinal observation will be necessary to confirm the above speculation.

PD signals with GS thickening of synovial tissues in RA patients reflect synovial cell hyperplasia with neovascularization [31, 32]. Therefore, high serum concentrations of MMP-3, RANKL, and angiogenesis factors along with acute phase reactants are commonly observed in patients with RA [33–35]. In this regard, we and other investigators have revealed increments of serum VEGF, angiopoietin-1 and angiopoietin-2 in RA patients that are correlated with clinical disease activity [36, 37]. Scirè et al. [14] previously reported a correlation of PD measures with CRP in patients with early stage RA, although this correlation was very low compared with active disease. In comparison with the results by Scirè et al. [14], in the present study CRP, ESR, MMP-3, VEGF, angiopoietin-2 and RANKL remained in the normal ranges regardless of the presence or absence of subclinical PD synovitis. Furthermore, in the present study there were no correlations between PD scores and CRP, ESR, MMP-3, VEGF, angiopoietin-2 or RANKL. Since all of the present cases achieved more stringent remission as compared with the cases in the report by Scirè et al. [14], no correlation could be determined. At this point, the presence of US bone erosion or a higher GS score is believed to be a very relevant finding for predicting the presence of subclinical PD synovitis in patients who have achieved definitive clinical remission. Alternatively, the use of conventional biomarkers may not be enough to identify remnant disease activity, and more global analysis may be warranted to seek the biomarkers that differentiate the presence or absence of imaging remission.

There are some limitations in the present study. We were unable to validate the multivariate analysis, probably due to the small sample size. Also, this is not a randomized controlled trial but an observational study, therefore the choice of DMARDs depended on each physician’s preference. These differences might affect the distribution of subclinical PD synovitis. Larger-scale randomized controlled trials are needed to confirm our present findings. However, as stated by the Targeted Ultrasound Initiative Group [38], the suppression of residual PD synovitis is suggested as a target to achieve in imaging remission. Thus our present data may emphasize the importance of subclinical PD synovitis and suggest that it may be an ideal surrogate marker in attempts to achieve complete remission in patients with RA, especially in the earlier stages of the disease, although longitudinal studies containing plain radiographic progression are necessary to clarify the findings of the present study.

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**Fig. 1** Correlation between total PD score and serum biomarkers.

No correlation between total PD score and any of the biomarkers was observed. Correlations were assessed with Spearman’s correlation coefficient. Ang-2, angiopoietin-2.
Power Doppler (PD) subclinical synovitis may be an ideal surrogate marker to for complete remission of RA.

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

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