Meta-analysis

Prevalence of ultrasound-detected residual synovitis and risk of relapse and structural progression in rheumatoid arthritis patients in clinical remission: a systematic review and meta-analysis

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Abstract

Objectives. The aims of this study were to assess the prevalence of US-detected residual synovitis in patients with RA in clinical remission (CR) and evaluate its predictive value for relapse and structural progression.

Methods. We performed a systematic literature search of Medline, Embase and rheumatology meeting databases from 1 January 2001 to 28 May 2012. The prevalence of US grey-scale (USGS) signals (synovial hypertrophy or joint effusion) and power Doppler (PD) signals were collected, taking into account CR definitions [44-joint DAS (DAS44), 28-joint DAS (DAS28), SDAI, ACR 1981 or ACR/European League Against Rheumatism 2011], stage of RA (early or long-standing) and US examination (from 5 to 44 joints assessed). A meta-analysis assessing the risk of relapse or structural progression in patients with synovitis involved the Mantel-Haenszel method.

Results. We included 19 studies of 1618 patients, 1369 in remission. The prevalence of USGS positive (USGS+), USGS+/PD negative (PD–), USGS+/PD positive (PD+) and USGS negative (USGS–/PD–) was 84%, 41%, 44% and 15%, respectively. The prevalence of USGS+ or USGS+/PD+ was comparable among CR definitions and US methods. The prevalence of USGS+ and USGS+/PD+ was greater for long-standing than early RA (P < 0.001). Meta-analyses of five studies (271 patients), three studies (173 patients) and two studies (798 joints) revealed an association of USGS+/PD+ and risk of relapse [odds ratio (OR) 3.2 (95% CI 1.8, 5.9), \( P = 0.001 \), \( I^2 = 0\% \)] and structural progression in individual patients [OR 9.13 (95% CI 1.1, 74.3), \( P = 0.04 \), \( I^2 = 43\% \)] and joints [OR 6.95 (95% CI 3.4, 13.9), \( P < 0.0001 \), \( I^2 = 6\% \)] over 1-2 years.

Conclusion. US-detected residual synovitis is frequent and predicts the risk of relapse and structural progression in RA patients with CR.

Key words: prevalence, prognostic factors, remission, rheumatoid arthritis, synovitis, ultrasound, meta-analysis, systematic review.

Introduction

RA is an inflammatory rheumatism that leads to joint inflammation and destruction. The prognosis has profoundly changed over the past 15 years with new biologic therapies that can prevent structural damage [1]. According to the European League Against Rheumatism (EULAR) recommendations [2], remission or low disease activity is the treatment aim for RA because joint damage presumably does not progress in patients in
clinical remission (CR) [3, 4]. Several criteria of remission have been developed in the last decade; all are composite criteria based on clinical outcomes such as swollen joint count, tender joint count, patient global assessment, physician global assessment and ESR or CRP level [ACR, 28-joint DAS (DAS28), 44-joint DAS (DAS44), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and ACR/EULAR 2011]. However, patients with RA in remission by any established criteria can exhibit radiographic progression. Recently an observational cohort showed that in patients with CR based on criteria such as ACR/EULAR 2011, SDAI, CDAI remission and DAS28-CRP could exhibit radiographic progression at 20%, 24%, 19% and 30%, respectively [5].

US is a non-invasive, inexpensive and easily accessible tool that is more sensitive for detecting synovitis [6–8] and better predictive of structural damage than clinical examination [3, 4]. The EULAR 2013 recommendations mention the role of imaging in detecting persistent inflammation in patients in CR and subsequent prediction of outcomes [9]. However, the US assessment of RA activity in terms of the modality of examining joints lacks consensus [10]. Some studies showed that patients in CR could have residual synovitis, which is associated with disease activity and progression [4, 11–13].

The aim of this work was to assess the prevalence of US-detected residual synovial hypertrophy in RA patients in CR through a systematic literature review. We also aimed to evaluate the impact of the modality of US joint examination, disease duration or remission criterion used on this prevalence. A meta-analysis was conducted to assess the association of US-detected synovial hypertrophy with power Doppler (PD) positivity and risk of structural damage and relapse.

Materials and methods

Study design

This study was a systematic review of reports assessing US-detected residual synovitis in patients with RA in CR.

Search strategy

A systematic search was conducted using Medline and Embase with the following search terms: arthritis, rheumatoid/ultrasoundography (Majr: noexp) for Medline and rheumatoid AND (arthritis/exp/mj OR arthritis/mj) AND (ultrasoundography/exp/mj OR ultrasoundography/mj) AND (article/it OR conference abstract/it) for Embase.

The research was limited to articles of studies of adults >18 years of age published in English or French from 1 January 2001 to 28 May 2012 and in priority journals within Embase. Case reports and reviews were excluded. The literature search was performed on 28 May 2012. We also manually searched references of relevant articles, review papers and abstracts presented at ACR annual scientific meetings, the EULAR annual congress and the French Society of Rheumatology scientific meetings published from 2006 to 2012.

Selection of articles

We included studies assessing early or long-standing RA in CR with US evaluation. Exclusion criteria included lack of US or clinical disease activity evaluation, US clinical association, reviews or case reports. For longitudinal studies in which the predictive values of residual synovitis for relapse or structural progression were a concern, the validity of included studies for meta-analysis was assessed by a predefined methodological checklist [14]. Quality of evidence was evaluated for studies included in the meta-analysis by judging six areas of potential study biases related to study participation, study attrition, measurement of prognostic factors, measurement of and control of confounding variables, measurement of outcomes and analysis approaches.

Data extraction

A standardized data collection form was generated on the basis of a review of the literature and was tested with a sample of 10 articles. The data were extracted by two of the authors (H.N. and A.R.-W.) who used a predetermined form; differences were resolved by consensus. The following data were recorded: general information about the studies (i.e. authors, year of publication, journal, definition of CR [i.e. DAS, DAS28, ACR, SDAI, CDAI, ACR/EULAR 2011], stage of RA [early, ≤2 years; long-standing disease, >2 years]), characteristics of the included population [age, sex, disease duration, DASs, ESR, CRP, RF, ACPA, DMARDs and biologic agents], US examination method [number of joints assessed, method of scoring (binary, semi-quantitative, OMERACT score), definition of synovial hypertrophy and definition of a PD-positive (PD+) signal)]. For the final analysis, data on frequency of synovitis with only a semi-quantitative method were transformed to binary values in terms of synovial hypertrophy (grade >0 or 1) by a semi-quantitative scoring method (US grey-scale–positive signal (USGS+)), synovial hypertrophy with no PD signal (USGS+/PD−), active synovitis defined by synovial hypertrophy with a positive PD signal or grade >0 or 1 with a semi-quantitative method (USGS+/PD+) and normal joints (USGS−/PD−). The definition of CR was a DAS <1.6, DAS28 (either DAS28-ESR or DAS28-CRP) with different cut-off values accepted as indicative of remission from 2.3 to 2.6, SDAI with different cut-off values accepted as indicative of remission from 3.3 to 5, ACR (five of six criteria satisfied on separate occasions 2 months apart), ACR/EULAR 2011 [all ≤1: tender 28-joint count, swollen 28-joint count, CRP (in mg/dl) and patient global visual analogue scale (0–10 cm)]. When the same population was studied and reported in several publications, the most informative publication was included in the review.

For longitudinal studies, additional data were collected: duration and treatment during follow-up, frequency of relapse and structural progression. Relapse was defined as (i) an increase in disease activity with non-fitting CR criteria or flares and (ii) requiring an initiation, change or increase in therapy. In studies with a prospective follow-up,
the corresponding authors were contacted if data were missing for the analysis.

Statistical analysis

A descriptive analysis of the extracted data was performed. The results are presented as mean (s.d.) or percentages. The prevalence of USGS+, USGS+/PD−, USGS+/PD+ and USGS−/PD− was compared by disease duration (early or long-standing RA), CR criterion used and number of joints assessed by US. For descriptive objectives, prevalences were calculated at the patient level.

We performed a meta-analysis assessing the association of USGS+/PD+ disease and risk of relapse and structural progression. The association of baseline clinical joint assessments and structural progression in individual joints was also evaluated. We used joints because comparable data for each imaging modality were available for each patient. We calculated the odds ratios (ORs) and 95% CIs with the Mantel–Haenszel method and a fixed-effects model. Heterogeneity was tested with Cochran’s Q test [16]. If > 50% indicated significant heterogeneity ($I^2 > 25\%$, 50% and 75% corresponded to low, medium and high heterogeneity, respectively). In the case of heterogeneity, a random-effects model was used. When heterogeneity persisted with a random-effects model, reports were classified by their methodological quality and reports with low quality were excluded. Otherwise, a fixed-effects model was used. Meta-analyses involved RevMan 5 (Nordic Cochrane Centre, Copenhagen, Denmark) and additional analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA) and Microsoft Excel 2010 (Microsoft, Redmond, WA, USA).

Results

Selection of studies for the meta-analysis

We identified 294 articles from Medline and 310 from Embase. We excluded 582 articles after reading the titles and abstracts and found only 22 full-text articles potentially eligible. In addition, we found four extra studies by manual search. After analysis of 26 articles, we retained only 13 articles for analysis. We added six other studies with relevant details not duplicated with published full texts, but only abstracts were added from rheumatology international meetings. The literature review process is shown in Fig. 1.

Study characteristics

Characteristics of included studies are summarized in Table 1. In all, 19 studies included 1618 patients: 2 were of recently diagnosed RA (<2 years) [15, 16] and 17 were of early and long-standing RA (including 1 [17] comparing early and long-standing RA); in 6 studies [12, 15, 16, 18-20] CR was described in a subgroup of RA patients and 13 studies included only RA patients in CR. We analysed 7 cross-sectional studies [11, 16, 18, 21-24] and 12 longitudinal studies (cohorts or case studies); 8 concerned prognostic values of US [12, 15, 17, 25-29]. Among these eight studies were five concerning the outcome or relapse [12, 15, 17, 26, 27] and four concerning structural progression [12, 25, 28, 29]. We evaluated the quality of prognostic study for these eight studies, all with a score of at least 4 of 6 (see Table 1 and see supplementary Table S1, available at Rheumatology Online).

For 15 of 19 studies [11, 12, 15-18, 20, 21, 25-31] the semi-quantitative US definition (0–3) or the OMERACT definition was used, and for 4 studies [19, 22-24] a binary definition was used (synovitis: yes/no). For 7 of 19 studies, reproducibility was evaluated at least with inter-reader evaluation. Concerning the joints of interest, seven studies [17, 20, 25-27, 30, 31] (including 671 patients) assessed only one hand, six [11, 12, 18, 19, 28, 29] (315 patients) assessed two hands with or without the MTP joints and 6 [15, 16, 21-24] (383 patients) explored many sites (28, 42 or 44 articulations and 1 [23] of 12 sites including the elbows, wrists, second and third MCP joints, knees and ankles).

Characteristics of the study populations included in the selected studies

Among 1618 patients included in the studies, 1369 were in CR. Patient characteristics are described in Table 2.

Prevalence of US-detected synovitis in RA patients in CR

The prevalence of USGS+, USGS+/PD−, USGS+/PD+ and USGS−/PD− was 81.8%, 40%, 43% and 15.7%, respectively. USGS+ and USGS+/PD+ prevalence was comparable among the different definitions of CR (DAS44, DAS28, SDAI, ACR 1981 or ACR/EULAR 2011) and US examination methods (from 5 to 44 joints assessed) (Fig. 2A and B). The prevalence of USGS+ and USGS+/PD+ was higher for patients with long-standing vs early RA (87% of USGS+ compared with 64%, $P < 0.001$ and 45% of USGS+/PD+ compared with 34%, $P < 0.001$) (Fig. 2C).
### Table 1: Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Disease duration, years</th>
<th>Remission criteria</th>
<th>US studied joints</th>
<th>Component studies</th>
<th>US definition</th>
<th>QoPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balsa et al.</td>
<td>2010</td>
<td>97</td>
<td>ID, 5.9</td>
<td>DAS28, SDAI, ARA</td>
<td>42; multiple sites</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Balsa et al.</td>
<td>2011</td>
<td>100</td>
<td>ID</td>
<td>SDAI, ACR/EULAR</td>
<td>42; multiple sites</td>
<td>GS, PD</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Peiteado et al.</td>
<td>2010</td>
<td>101</td>
<td>ID</td>
<td>DAS28, SDAI</td>
<td>42; multiple sites</td>
<td>GS, PD</td>
<td>B</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>2006</td>
<td>124</td>
<td>ID, 7</td>
<td>PO, DAS28, ACR</td>
<td>5; wrist +2-5 MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>2008</td>
<td>102</td>
<td>ID, 7</td>
<td>PO, DAS28, ACR</td>
<td>5; wrist +2-5 MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Foltz et al.</td>
<td>2012</td>
<td>85</td>
<td>ID, 2.9</td>
<td>DAS</td>
<td>14; wrists +2,3,5 MCPs + 2,3,5 MTPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Peluso et al.</td>
<td>2011</td>
<td>94</td>
<td>48 early, 46 late</td>
<td>DAS</td>
<td>10; wrist +2,3 MCPs, 2,3 PIPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Raffeiner et al.</td>
<td>2011</td>
<td>109</td>
<td>ID</td>
<td>DAS28</td>
<td>32; wrists + MCPs + PIPs + MTPs</td>
<td>PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Ravagnani et al.</td>
<td>2010</td>
<td>42</td>
<td>ID</td>
<td>DAS28</td>
<td>22; wrists + MCPs + PIPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Saleem et al.</td>
<td>2009</td>
<td>100</td>
<td>ID, 9</td>
<td>DAS28</td>
<td>6; wrist + MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Saleem et al.</td>
<td>2010</td>
<td>47</td>
<td>27 early, 20 late</td>
<td>DAS28</td>
<td>6; wrist + MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Saleem et al.</td>
<td>2011</td>
<td>128</td>
<td>ID, 8</td>
<td>DAS28, SDAI, ACR</td>
<td>5; wrist +2-5 MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Saleem et al.</td>
<td>2012</td>
<td>93</td>
<td>ID, 7</td>
<td>PO, DAS28, SDAI, ACR, ACR/EULAR</td>
<td>6; wrist + MCPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Sakellaridou et al.</td>
<td>2011</td>
<td>166</td>
<td>ID</td>
<td>DAS28, SDAI, ACR, ACR/EULAR</td>
<td>12; wrists + MCPs</td>
<td>PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Scirè et al.</td>
<td>2009</td>
<td>106</td>
<td>Early, 1.8</td>
<td>DAS</td>
<td>44, multiple sites</td>
<td>GS, PD</td>
<td>SQ</td>
<td>B</td>
</tr>
<tr>
<td>Senabre et al.</td>
<td>2011</td>
<td>33</td>
<td>ID, 7.3</td>
<td>DAS28</td>
<td>12; multiple sites: elbows, wrists, 2,3 MCPs, knees, ankle</td>
<td>GS, PD</td>
<td>SQ</td>
<td>OMERACT</td>
</tr>
<tr>
<td>Spinella et al.</td>
<td>2011</td>
<td>54</td>
<td>ID</td>
<td>DAS28, ACR</td>
<td>22; wrists + MCPs + PIPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td>B</td>
</tr>
<tr>
<td>Wakefield et al.</td>
<td>2007</td>
<td>10</td>
<td>Early, 1.7</td>
<td>DAS28</td>
<td>42; multiple sites</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td>Yoshimi et al.</td>
<td>2012</td>
<td>27</td>
<td>ID, 5</td>
<td>DAS28</td>
<td>22; wrists + MCPs + PIPs</td>
<td>GS, PD</td>
<td>SQ</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1618</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The quality of prognostic studies (QoPS) for the longitudinal study in which the predictive values of residual synovitis for relapse or structural progression are of concern (see supplementary data, available at Rheumatology Online). The score indicates the total of response Yes of the quality appraisal checklist developed by Hayden et al. [14], which indicates that the study has been designed and conducted in such a way as to minimize the risk of bias for that item. ID: indifference (mixed with early and long-standing rheumatoid arthritis); DAS28: 28-joint DAS; EULAR: European League Against Rheumatism; PO: remission based on physician’s opinion; B/SQ: binary/semi-quantitative; SDAI: simplified disease activity index; PD: power Doppler; GS: grey scale.
Long-term risk of relapse assessment for RA patients in CR

We performed a meta-analysis of five studies (271 patients) to assess the long-term risk of relapse in patients in CR. The characteristics of the studies are described in supplementary Table S2, available at Rheumatology Online. Substantial heterogeneity was detected, with $I^2 = 49\%$ ($P = 0.10$), even with a random-effects model. Regarding the methodology, one study was significantly different from the others in terms of disease duration (early compared with established in other studies) and follow-up duration (6 months compared with 12–24 months; see supplementary Table S2, available at Rheumatology Online). After excluding this study, the meta-analysis did not identify any heterogeneity ($I^2 = 0\%$, $P = 0.45$), but showed an association of USGS+/PD+ and risk of relapse [OR 3.2 (95% CI 1.8, 5.9), $P = 0.000$; Fig. 3].

The sensitivity and specificity of USPD to predict the risk of relapse ranged from 40% to 86% and 45% to 91%, respectively. The positive and negative predictive value of USPD+ at baseline was 34–71% and 38–92%, respectively (see supplementary Table S3, available at Rheumatology Online).

Risk of long-term structural progression for RA patients in CR

The risk of long-term structural progression by US findings for patients in CR was available for three studies (173 patients) and two studies (798 joints) assessed structural progression at the patient and joint level, respectively. The characteristics of the studies are shown in supplementary Table S4, available at Rheumatology Online. The meta-analyses identified increased risk of structural progression at the patient level [OR 9.13 (95% CI 1.1, 74.3), $P = 0.04$], with significant heterogeneity even with a random-effects model ($I^2 = 43\%$, $P = 0.18$), and the joint level [OR 6.95 (95% CI 3.4, 13.9), $P < 0.0001$], with significant heterogeneity even with a random-effects model ($I^2 = 6\%$, $P = 0.3$) (Fig. 4A and B). Moreover, three studies [12, 25, 28] analysed the association of the number of US-detected synovitis locations included in a US score and the risk of structural progression; all found a significant association between the number of US-detected synovitis locations and disease progression.

Discussion

The EULAR recommendations recently highlighted the importance of remission as an outcome [32]. For 12 years the DAS28 was the principal tool used to assess CR. Preventing structural damage is better with tight control based on DAS28 assessment than routine care [33]. New remission criteria were developed after an ACR and EULAR initiative aimed at more stringency. However, previous studies found that a patient could have CR (DAS28 < 2.6) but persisting synovitis [11, 31, 34]. Imaging techniques such as US and MRI can directly visualize both synovitis and bone damage and are more sensitive than clinical examination [14, 33]. In our systematic review, the prevalence of synovial hypertrophy with a Doppler signal in CR was significant, at 44%. This finding is a consequence of the lack of sensitivity of clinical examination to detect levels of inflammation objectively demonstrated by imaging.

### Table 2: Characteristics of the population

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients in remission, n</th>
<th>Age, years</th>
<th>Sex, male, %</th>
<th>Disease duration, years</th>
<th>RF positive, %</th>
<th>ACPA positive, %</th>
<th>DMARDs, %</th>
<th>Biologic agent, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balsa et al. [21]</td>
<td>97</td>
<td>56.1</td>
<td>28</td>
<td>5.9</td>
<td>64</td>
<td>70</td>
<td>92</td>
<td>7</td>
</tr>
<tr>
<td>Balsa et al. [22]</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Peiteado et al. [24]</td>
<td>101</td>
<td>53.0</td>
<td>28</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Brown et al. [20]</td>
<td>107</td>
<td>56.0</td>
<td>52</td>
<td>7</td>
<td>64</td>
<td>NA</td>
<td>92</td>
<td>4.6</td>
</tr>
<tr>
<td>Brown et al. [25]</td>
<td>102</td>
<td>57.0</td>
<td>33</td>
<td>7</td>
<td>64</td>
<td>NA</td>
<td>99</td>
<td>2</td>
</tr>
<tr>
<td>Foltz et al. [12]</td>
<td>47</td>
<td>51.9</td>
<td>33.6</td>
<td>2.9</td>
<td>63.5</td>
<td>51.1</td>
<td>96.5</td>
<td>20</td>
</tr>
<tr>
<td>Peluso et al. [17]</td>
<td>94</td>
<td>51.4</td>
<td>19.1</td>
<td>5.1</td>
<td>63.8</td>
<td>58.5</td>
<td>45.1</td>
<td>65.9</td>
</tr>
<tr>
<td>Raffeiner et al. [29]</td>
<td>109</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>100</td>
</tr>
<tr>
<td>Ravagnani et al. [18]</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
<td>100</td>
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<td>Saleem et al. [30]</td>
<td>100</td>
<td>57.0</td>
<td>39</td>
<td>9</td>
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<td>NA</td>
<td>50</td>
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<tr>
<td>Saleem et al. [27]</td>
<td>47</td>
<td>53.0</td>
<td>48.9</td>
<td>5.2</td>
<td>44.3</td>
<td>38.6</td>
<td>57.4</td>
<td>42.6</td>
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<tr>
<td>Saleem et al. [31]</td>
<td>128</td>
<td>54.0</td>
<td>NA</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>52</td>
<td>48</td>
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<tr>
<td>Saleem et al. [26]</td>
<td>93</td>
<td>56.6</td>
<td>42.3</td>
<td>7</td>
<td>41.9</td>
<td>59.4</td>
<td>90</td>
<td>0</td>
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<td>Sakellariou et al. [19]</td>
<td>56</td>
<td>59.0</td>
<td>27</td>
<td>NA</td>
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<td>NA</td>
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<td>100</td>
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<td>Scirè et al. [15]</td>
<td>43</td>
<td>59.5</td>
<td>41</td>
<td>1.8</td>
<td>39</td>
<td>29</td>
<td>93.4</td>
<td>2.8</td>
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<tr>
<td>Senabre et al. [23]</td>
<td>33</td>
<td>60.0</td>
<td>27</td>
<td>7.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spinella et al. [11]</td>
<td>54</td>
<td>NA</td>
<td>19</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Wakefield et al. [16]</td>
<td>9</td>
<td>52.5</td>
<td>50</td>
<td>1.7</td>
<td>80</td>
<td>NA</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Yoshimi et al. [28]</td>
<td>22</td>
<td>53.9</td>
<td>13</td>
<td>5</td>
<td>74</td>
<td>NA</td>
<td>90</td>
<td>41</td>
</tr>
<tr>
<td>Total/mean</td>
<td>1369</td>
<td>55.4</td>
<td>33.7</td>
<td>6.4</td>
<td>59.0</td>
<td>55.3</td>
<td>75.2</td>
<td>35.3</td>
</tr>
</tbody>
</table>

NA: not available.
In this systematic study, the prevalence of synovial hypertrophy and a PD signal was higher in long-standing vs early RA. This finding could reflect that synovial tissue can become chronically thickened and less reversible in long-standing RA [17].

In terms of the prevalence of synovial hypertrophy and PD signals in RA patients in CR, US of the dominant hand might be achievable; the prevalence of synovitis in the dominant hand is comparable to that in several more joints. In fact, six of our studies evaluated the dominant hand and all were studies from the same team in the UK [20, 25–27, 30, 31]. The question is always the group of joints to evaluate, for which we lack consensus. In a French study, while evaluating several US scoring systems for synovitis and comparing to clinical examination, the authors evaluated all MCP and MTP joints (20 joints), the 28 joints of the DAS and the DAS28 joints and 10 MTP joints (38 joints) [35]. A Spanish team is more supportive of the simplified 12-joint PDUS model (wrist, MCP2, MCP3, knee, ankle, and elbow evaluated bilaterally) [36] and a German group is working on its German US7 score (seven joints, including wrist, MCP2, MCP3, PIP2, PIP3, MTP2 and MTP5 of the clinically dominant hand and foot) [37]. The systematic analysis of Mandl et al. [10] revealed that the seven joints included were good candidates for evaluating disease activity and responsiveness, even if sensitivity to change was inferior to the 12-joint score used in that database. We strongly support the one-hand US evaluation because it is feasible in clinical practice to correctly assess the synovial hypertrophy and PD signal and estimate the risk of relapse or structural progression, as shown in three of the six studies [25–27]. We still await the OMERACT US group synovitis scoring system in an ongoing multicentre European study to propose a standardized and reliable US synovitis global OMERACT scoring system.

Radiographic progression continues in RA patients in CR independent of the clinical criteria used [38]. In our study, the PD signal predicted clinical relapse and progression at the patient and joint level. The persistence of residual synovitis in patients in CR may explain the structural progression in these patients. This finding is consistent with the 2013 EULAR recommendations that US can detect inflammation that predicts subsequent joint damage even with CR and can be used to assess persistent inflammation [9].

A new outcome including US could be proposed, especially when a one-dominant-hand check might be sufficiently informative and applicable in routine practice. Outcomes may be superior by targeting therapy to PD activity rather than clinical targets alone. This situation might lead to the introduction of a new randomized trial using targeted US-detected remission in RA. In clinical practice, in patients with CR, US could be regularly performed and a persistent PD signal should signal caution when considering treatment.

We may have missed relevant studies that are not accessible or falsely indexed. However, our search results were thoroughly reviewed; we cross-checked references of papers dealing with this topic, international congress archives and books of abstracts from 2006 to search for unpublished potential articles. In addition, we contacted the authors of meeting abstracts for further information.

Concerning the limitations of this study, the article selection/inclusion process results in only a few studies...
being examined, several of them from the same author. While this is due in part to constraints on characteristics the articles must have in order to be relevant to the question being asked in the meta-analysis, the resulting narrow selection of articles is of concern. However, our search of the literature of RA in CR revealed only recent studies, so the obstacle of heterogeneity in both clinical and US assessment for systematic analysis [10] was overcome.

Because of the publication of the preliminary OMERACT definitions [39], synovitis was defined, all articles evaluated PD rather than colour Doppler signals and almost all articles adopted the definition of PD activity proposed by Szkudlarek et al. [40].

This is the first meta-analysis to study the impact of US-detected residual synovitis on structural progression and relapse. Additional research and replication is needed, including more studies and adopting more homogeneous models of structural progression, especially evaluating functional outcomes and quality of life.

Rheumatology key messages
- US-detected residual synovitis is highly prevalent in patients with RA in clinical remission.
- Power Doppler positivity of residual synovitis on US is associated with risk of relapse and structural progression in RA.

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

Supplementary data
Supplementary data are available at Rheumatology Online.

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2. Smolen JS, Landewe R, Breedveld FC et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying


