Subclinical Synovitis Assessed by Ultrasound Predicts Flare and Progressive Bone Erosion in Rheumatoid Arthritis Patients with Clinical Remission: A Systematic Review and Metaanalysis

Jingjing Han, Yan Geng, Xuerong Deng, and Zhuoli Zhang

ABSTRACT. ***Objective.*** Subclinical synovitis can be detected by ultrasound in patients with rheumatoid arthritis (RA) who are in clinical remission. We aimed to confirm its predictive value for flare and progressive bone erosion.

Methods. A systematic literature search was performed in Pubmed, Web of Science, Embase, and Cochrane Library on September 7, 2014. Baseline clinical and ultrasonographic characteristics were collected. Methodological quality was assessed. Pooled OR were calculated using Mantel-Haenszel model. We explored the source of heterogeneity through subgroup analysis and completed a cumulative metaanalysis.

Results. Thirteen articles were included (8 with flare, 4 with bone erosion, 1 with both flare and bone erosion). Metaanalysis revealed an association between power Doppler (PD) positivity and the risk of flare (OR 4.52, 95% CI 2.61–7.84, $p < 0.00001$, $I^2 = 21\%$), the risk of progressive bone erosion on patient level (OR 12.80, 95% CI 1.29–126.81, $p = 0.03$, $I^2 = 52\%$) and the risk of progressive bone erosion on joint level (OR 11.85, 95% CI 5.01–28.03, $p < 0.00001$, $I^2 = 0\%$). Further subgroup analysis showed a higher risk of flare in patients with a study period < 1 year (OR 19.98 vs 3.41). No significant differences were observed in the subgroup analysis in duration of remission, disease duration, and medications. Moreover, cumulative metaanalysis indicated the validation and an increasing accuracy of PD positivity in predicting flare since 2012.

Conclusion. Ultrasound-detected subclinical synovitis can predict the risk of flare and progressive bone erosion in RA patients with clinical remission. Additionally, the flare of RA tends to occur within a followup of 1 year. (J Rheumatol First Release October 1 2016; doi:10.3899/jrheum.160193)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ULTRASONOGRAPHY SYNOVITIS
REMISSION METAANALYSIS

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can lead to joint destruction or even deformity. Since 2010, the widespread treat-to-target strategy, aiming at clinical remission or low disease activity[1], has greatly improved the prognosis of RA. However, in patients in clinical remission, progressive bone erosion can still be detected[2,3] and subsequent uncertain relapse can also be observed. Hence, it is indicative of a possibility that clinical remission of RA may not be the true state of remission, and an underlying inflammation may exist in patients with RA who are in clinical remission.

Musculoskeletal ultrasound (US) is a highly sensitive, nonradioactive and easily accessed tool. With the help of US, many studies found subclinical synovitis in patients with RA who were in clinical remission[4,5]. Our previous study had also shown a prevalence of subclinical US synovitis whatever the criteria we used to define clinical remission[6]. In addition, many studies revealed that the subclinical synovitis assessed by US might have a predictive value for flare and progressive bone erosion[7,8,9,10]. Further, a related metaanalysis performed in 2012 had already confirmed this conclusion[11].

In our current study we performed another metaanalysis to demonstrate the association between subclinical US synovitis and the risk of flare or progressive bone erosion. Compared with the previous metaanalysis, we included

From the Department of Geriatrics, and the Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China.

Supported by Peking University Health Science Center, Peking University First Hospital, and The Capital Health Research and Development of Special (2011-4021-03), a non-profit organization.

J. Han, MD, Department of Geriatrics, Peking University First Hospital; Y. Geng, MD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital; X. Deng, MD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital; Z. Zhang, MD, PhD, Department of Rheumatology and Clinical Immunology, Peking University First Hospital.

Address correspondence to Dr. Z. Zhang, Department of Rheumatology and Clinical Immunology, Peking University First Hospital, No. 8 Xishiku St., Xicheng District, 100034 Beijing, China. E-mail: zhuoli.zhang@126.com

Accepted for publication August 30, 2016.

additional articles published in the last 2 years, gave a deeper explanation for heterogeneity using subgroup analysis, and accomplished a cumulative metaanalysis.

MATERIALS AND METHODS

Search strategy. A systematic search was conducted in Pubmed, Embase, Web of Science (including the conference part), and the Cochrane Library, using all spellings of "rheumatoid arthritis," "ultrasonography," and "remission" as keywords or medical subject headings. The article search was performed on September 7, 2014. We also manually searched the references of some related articles or reviews and included grey literature.

Selection of articles. We selected articles about the predictive value of subclinical synovitis for relapse or bone erosion in patients with RA who are in clinical remission. Cohort studies of adults (age > 18 yrs) published in English were included. We excluded articles that had different objectives or inaccessible crucial data, as well as cross-sectional studies, case reports, reviews, and consensus reports. The qualities of the enrolled articles were evaluated by the Quality in Prognosis Studies tool in the following 6 areas: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis[12].

Data extraction. The following data in the selected articles were recorded: general information (sex, age, disease duration, duration of remission before inclusion); baseline clinical characteristics [swollen joint count, tender joint count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anticyclic citrullinated peptide antibodies, 28-joint Disease Activity Score (DAS), Health Assessment Questionnaire score, shared epitope]; baseline US characteristics [scoring system, scanning region, power Doppler score, greyscale (GS) score, and cutoff points for US synovitis]; followup information (study period, medications); diagnostic criteria and remission criteria of RA; definition and outcome of flare; and definition and outcome of progressive bone erosion. Corresponding authors were contacted if crucial data could not be obtained in the full text.

The literature search, quality assessment, and data extraction were performed independently by 2 authors (J.H. and Y.G.). Differences were discussed and consulted with Z. Zhang.

Statistical analysis. The association of baseline US characteristics and the outcome of flare or progressive bone erosion were calculated by OR in patient level and joint level if data for each joint were available. Mantel-Haenszel model and random effect method were used. I^2 was adopted to represent heterogeneity ($I^2 \le 25\%$, low; $25\% < I^2 \le 50\%$, medium; $I^2 > 50\%$, high). Further, in articles related to flare, we analyzed the sources of heterogeneity in 4 subgroups: disease duration, duration of remission before baseline, length of followup period, and medications during followup. We also did a cumulative metaanalysis. A 2-sided $p < 0.05$ ($p < 0.1$ in the test for heterogeneity) was regarded as a significant difference. Metaanalysis was done with Revman 5.2 (The Nordic Cochrane Centre). Cumulative metaanalysis was done with STATA 11.0 (Stata Corp.).

The research protocol was approved by Peking University First Hospital Institutional Review Board for clinical research (2014[785]).

RESULTS

Study characteristics. Our literature search yielded 105 articles in Pubmed, 180 articles in Web of Science, 411 articles in Embase, and 97 articles in the Cochrane Library. In addition, 1 reference and 1 unpublished article (i.e., 1 piece of grey literature) were identified as eligible. After reviewing the titles, abstracts, and full texts, we finally included 13 articles (Figure 1). Among them, 10 articles (including 1 piece of grey literature) were full texts[3,7,8,9,10,13,14,15,16], 3 had only abstracts available[17,18,19], 8 were related to flare, 4 were related to bone erosion, and 1 was related to both flare and bone erosion. Compared with the previous metaanalysis, 5 additional articles were written or published in the last 2 years (including 1 piece of grey literature).

The RA diagnostic criteria in 10 of the 13 articles were 1987 American College of Rheumatology (ACR) criteria, while the other 3 (including 1 piece of grey literature) used 2010 ACR/European League Against Rheumatism criteria[8,16]. As for the remission criteria, all the articles applied DAS criteria, although the cutoff points were different. US examinations of the dominant hand and wrist were done in all study participants, of which 10 studies additionally examined the bilateral hands. Several studies further scanned metatarsophalangeal joints, knees, or other joints. US data were all evaluated by a semiquantitative scale from 0 to 3 except for 1 article using a dichotomous measure[15]. Power Doppler scores were obtained in all 13 articles. GS scores were assessed in 5 articles (including 1 piece of grey literature)[3,7,8,14]. In most of the selected articles, flare was defined as the increase of disease activity, Sharp score was chosen to evaluate the progression of bone erosion, and quality scores calculated by the Quality in Prognosis Studies tool were above 4. The characteristics of the studies and patients in this metaanalysis are described in Table 1 and Table 2; and in Supplementary Table 1 and Supplementary Table 2, available online at jrheum.org.

US and risk of flare. The relapse rate mainly ranged from 22.7% to 51.4% in the 9 selected articles related to risk of flare. The metaanalysis of these 9 studies (including 4 additional studies compared with the previous metaanalysis) showed an association of US PD positivity and risk of flare in patients with RA in clinical remission (pooled OR 4.52, 95% CI 2.61–7.84, $p < 0.00001$; Figure 2). A heterogeneity of $I^2 = 21\%$ was also detected ($p = 0.25$). In the 4 studies that assessed GS scores, metaanalysis showed a risk of flare in patients with US GS positivity (pooled OR 3.69, 95% CI 1.71–7.93, $p < 0.0008$; Supplementary Figure 1, available online at jrheum.org), with a low heterogeneity ($I^2 = 5\%$, $p = 0.37$). Therefore, US PD and GS positivity could increase the risk of flare in patients with RA who are in clinical remission.

US and risk of progressive bone erosion. Three articles were related to progression of bone erosion. A pooled OR of 12.80 (95% CI 1.29–126.81, $p = 0.03$) was discovered in the association between US PD positivity and risk of radiological progression (Figure 3A). The heterogeneity was $I^2 = 52\%$ ($p = 0.13$). At joint level, there was also a risk of progression in patients with US PD positivity (pooled OR 11.85, 95% CI 5.01–28.03, $p < 0.00001$; Figure 3B). No evidence of heterogeneity was found in joint level ($I^2 = 0\%$, $p = 0.97$). Hence, whatever the levels in patients or joints, US PD positivity could increase the risk of progressive bone erosion in patients with RA who have clinical remission.

Subgroup analysis of the risk of flare. In consideration of the heterogeneity in 9 articles related to flare, we further performed subgroup analysis based on our clinical experience.

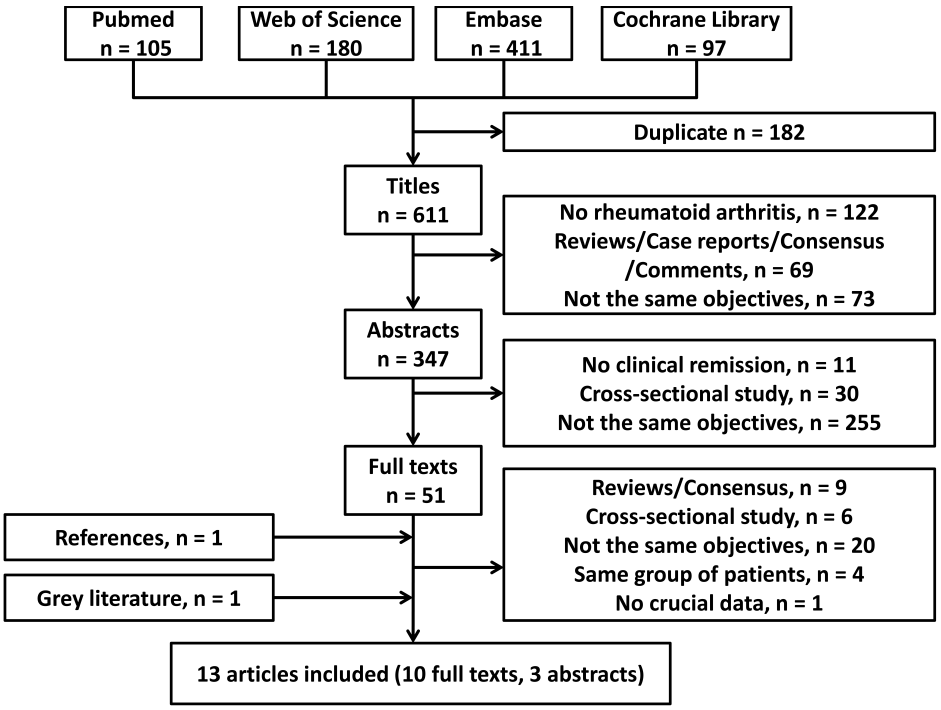


Figure 1. Flowchart of literature search.

The cutoff point in the subgroup of study period was 1 year (Figure 4A). Six of 9 articles had a study period of at least 1 year, while the other 3 were < 1 year. Respectively, in these 2 subgroups, the pooled OR in the association between PD positivity and risk of flare were 3.41 (95% CI 2.07–5.63, $p < 0.00001$) and 19.98 (95% CI 5.65–70.60, $p < 0.00001$). There was no evidence of heterogeneity within either subgroup ($I^2 = 0\%$, $p = 0.74$; $I^2 = 0\%$, $p = 0.63$). The OR value in the group with the shorter study period was greater than that in the group with the longer study period, with a high and significant heterogeneity ($I^2 = 84.6\%$, $p = 0.01$) and no overlap in CI between subgroups. This indicates that patients with PD positivity in clinical remission were much more likely to relapse within 1 year of followup.

Six articles presented data about the duration of remission before baseline. They were divided into 2 subgroups at the cutoff point of 1 year (Figure 4B). Two studies having duration of remission longer than 1 year showed a risk of flare in patients with PD positivity (pooled OR 7.40, 95% CI 1.48–37.09, $p = 0.01$). Meanwhile, the metaanalysis of 4 studies with duration of remission < 1 year revealed a pooled OR of 4.89 in the association between US PD positivity and risk of flare (95% CI 1.48–16.18, $p = 0.009$). The heterogeneity was moderate to high ($I^2 = 45\%$, $p = 0.18$; $I^2 = 60\%$, $p = 0.06$) within each subgroup and was 0 between 2 subgroups ($I^2 = 0\%$, $p = 0.69$). Moreover, there was even an overlap in the CI of OR between 2 subgroups. Hence, no significant effect was found on the risk of flare in the subgroup of duration of remission.

The subgroup analysis of disease duration was done in 8 articles with a cutoff point of 5 years (Figure 4C). In the group of disease duration longer than 5 years, the meta-analysis of 5 related articles showed a risk of flare in patients with US PD positivity (pooled OR 3.99, 95% CI 2.34–6.80, $p < 0.00001$), and without any heterogeneity ($I^2 = 0\%$, $p = 0.62$). However, in the group of shorter disease duration (3 articles < 5 years), we found an association of risk of flare and PD positivity with no statistical significance (pooled OR 5.75, 95% CI 0.84–39.13, $p = 0.07$) and with a high heterogeneity ($I^2 = 72\%$, $p = 0.03$). Apart from that, no evidence of heterogeneity was detected between 2 subgroups ($I^2 = 0\%$, $p = 0.72$). So there was no significant effect on the risk of flare in the subgroup of disease duration.

As for the medications during followup, we grouped the 8 related articles according to the use of biologics (Figure 4D). Four studies admitted the use of biologics. The pooled OR of these 4 articles in the association between risk of flare and PD positivity was 3.94 (95% CI 1.94–8.00, $p = 0.0002$). Accordingly, the other 4 articles in the nonbiologics group had a pooled OR of 6.54 (95% CI 1.53–28.07, $p = 0.01$) and a high heterogeneity ($I^2 = 66\%$, $p = 0.03$). Further, no heterogeneity existed between the 2 subgroups ($I^2 = 0\%$, $p = 0.54$) and there was an overlap in the CI of OR within the 2 groups. As a result, no significant effect of medications on the risk of flare was observed in patients with RA who are in clinical remission.

Cumulative metaanalysis in the risk of flare. To clearly elucidate the effect of PD positivity on risk of flare, we

Table 1. Characteristics of the included studies on flare.

Author, Reference	No. Patients	Diagnostic Criteria	Remission Criteria	Definition of Flare	US Joints	US Evaluation	Cutoff Points in PD/GS	Study Period, mos	Medications	QIPS
Scire, 2009 [13]	106	1987 ACR	DAS < 1.6	DAS ≥ 1.6	Bilateral wrists, MCP, PIP, shoulders, elbows, sternoclavicular, acromioclavicular, knees, ankles, MTP joints	0-3*	PD > 0	6	cDMARD	5
Saleem, 2010 [14]	27	1987 ACR	DAS28 < 2.6	DAS28 > 2.6 or an increase of 1.2 if DAS < 2.6	Dominant wrist, MCP1-5, PIP1-5	0-3*	GS > 0; PD > 0	24	cDMARD	4
Peluso, 2011 [15]	94	1987 ACR	DAS < 1.6	DAS > 1.6	Bilateral wrists, MCP2-3, PIP2-3	Dichotomy	PD+, GS+	12	66% cDMARD + anti-TNF, others only cDMARD	4
Saleem, 2012 [7]	93	1987 ACR	DAS28 < 2.6 or SDAI ≤ 3.3 or 1981 ACR criteria or 2010 ACR criteria	Any increase in disease activity that required a change in therapy	Dominant wrist and MCP	0-3*	GS > 0; PD > 0	12	cDMARD	6
Foltz, 2012 [9]	47	1987 ACR	DAS < 2.4	DAS ≥ 2.4 or an increase in DAS that required a change in therapy or an increase of steroids > 10 mg/day	Bilateral wrists, MCP2/3/5, MTP2/3/5	0-3*	PD > 0	12	cDMARD, biologics, steroids (< 10 mg/day)	6
Iwamoto, 2014 [8]	42	1987 ACR, 2010 ACR/EULAR	DAS28 < 2.6	DAS > 3.2 and an increase in therapy	Bilateral shoulders, elbows, MCP, PIP, wrists, knees, ankles, MTP	0-3*	GS ≥ 14; PD ≥ 3	6	cDMARD, steroids (≤ 9 mg/day)	4
Geng, 2014	72	2010 ACR/EULAR	DAS28 (ESR) ≤ 2.6	DAS28 (ESR) > 2.6	Bilateral wrists, MCP1-5, PIP 1-5	0-3*	GS > 0; PD > 0	12	NA	4
Ramirez Garcia, 2014 [17]	28	NA	DAS28 < 2.6	NA	Bilateral wrists, MCP, PIP, knees	0-3*	PD > 0	12	cDMARD, 39.3% biologics	6
Van Der Ven, 2014 [18]	67	NA	DAS44 < 2.4 and SJC ≤ 1	DAS44 ≥ 2.4 or SJC > 1	Bilateral wrists, MCP2-5, PIP2-5, MTP2-5	0-3*	PD > 0	3	cDMARD + anti-TNF	4

* Semiquantitative. cDMARD: conventional disease-modifying antirheumatic drugs; NA: not available; US: ultrasound; PD: power Doppler; GS: greyscale; QIPS: Quality in Prognosis Studies tool; ACR: American College of Rheumatology; DAS: Disease Activity Score; MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; DAS28: 28-joint DAS; anti-TNF: tumor necrosis factor inhibitor; SDAI: Simplified Disease Activity Index; EULAR: European League Against Rheumatism; ESR: erythrocyte sedimentation rate; SJC: swollen joint count.

performed a cumulative metaanalysis. Results are shown in Supplementary Figure 2, available online at jrheum.org. Since 2012 there was a sustainable, significant association between risk of flare and PD positivity in patients with RA who are in clinical remission, and also a tendency of a narrow scale of CI on pooled OR. Therefore, the cumulative metaanalysis revealed an increasing predictive accuracy of US PD positivity on risk of flare in patients with RA who are in clinical remission.

DISCUSSION

Because the results in the previous single-center studies were inconsistent, the association between US PD positivity and the risk of flare/radiological progression was uncertain. For example, in the predictive value of flare, 3 of 9 articles showed a lack of predictive value of PD positivity on flare while the other 6 showed predictive OR that fluctuated from 3.55 to 28.80. To resolve this question, Nguyen, *et al*[11] did a metaanalysis and demonstrated a predictive value of US PD positivity for flare and progressive bone erosion in patients with RA who are in clinical remission. However, they excluded 1 article with a significant difference when encountering the problems of heterogeneity. In comparison with their work, our metaanalysis added 5 more articles published in recent years (i.e., included the largest number of articles ever before, to our knowledge), confirmed the definite predictive value of US PD positivity, and included a subgroup analysis to deeply explicate the heterogeneity.

The risk of flare in patients with PD positivity was 4.52 times as high as that in patients with PD negativity. This result was quite consistent with the pathogenesis of synovitis. Synovial angiogenesis, which can be sensitively detected by power Doppler US, is known as the essence of active synovitis[20]. Previous studies had also reported a high correlation between PD positivity and inflammatory cell infiltration or vascularity in synovial tissues (r = 0.84,

Table 2. Characteristics of the included studies on progressive bone erosion.

Author, Reference	No. Pts	Diagnostic Criteria	Remission Criteria	Radiographed Joints	Radiography Evaluation	Definition of Progression	US Joints	US Evaluation	Cutoff Points in PD/GS	Study Period, yrs	Medication	QIPS
Brown, 2008 [3]	102	1987 ACR	1981 ACR or DAS28 < 2.6	Hands, wrists, feet	Genant-modified Sharp score	Δ > SDC	Dominant wrist, MCP2-5	0-3*	PD > 0; GS > 0	1	cDMARD, steroids (≤ 5 mg/day)	6
Raffeiner, 2011 [19]	109	NA	DAS28	Hands, feet	van der Heijde/ modified Sharp score	ΔTSS > 0	Bilateral wrists, MCP, PIP, MTP	0-3*	PD > 0	1	Anti-TNF	4
Foltz, 2012 [9]	47	1987 ACR	DAS < 2.4	Hands, wrists, feet	van der Heijde/ modified Sharp score	ΔTSS ≥ 1	Bilateral wrists, MCP2/3/5, MTP2/3/5	0-3*	PD > 0	1	cDMARD, biologics, steroids (< 10 mg/day)	6
Yoshimi, 2013 [10]	31	1987 ACR	DAS28 ESR < 2.6 or DAS28 CRP < 2.3	Hands	van der Heijde/ modified Sharp score	ΔTSS > 0.5 U/yr	Bilateral wrists, MCP, PIP	0-3*	PD ≥ 2	2	cDMARD, anti-TNF, steroids (1-5 mg/day)	4
Ogishima, 2014[16]	77	1987 ACR or 2010 ACR/ EULAR	DAS28 CRP ≤ 2.3	Hands	Erosion and JSN assessment, but not van der Heijde/ modified Sharp score or Genant-modified Sharp score	Δ (erosion + JSN) > 0	Bilateral wrists, MCP1-5, PIP2-5	0-3*	PD > 0	282 ± 150 days	cDMARD, biologics, steroids (5.1 ± 2.5 mg/day)	3

* Semiquantitative. SDC: smallest detectable change; JSN: joint space narrowing; TSS: total Sharp score (sum of the assessment in erosion and JSN); US: ultrasound; NA: not available; PD: power Doppler; GS: greyscale; QIPS: Quality in Prognosis Studies tool; ACR: American College of Rheumatology; DAS: Disease Activity Score; MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; DAS28: 28-joint DAS; anti-TNF: tumor necrosis factor inhibitor; cDMARD: conventional disease-modifying antirheumatic drugs; EULAR: European League Against Rheumatism; CRP: C-reactive protein.

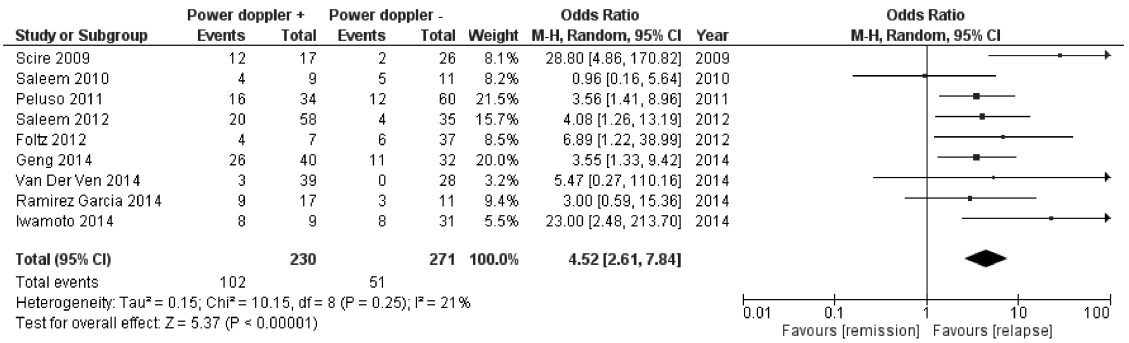


Figure 2. Summary of the association between ultrasonic power Doppler score and risk of flare.

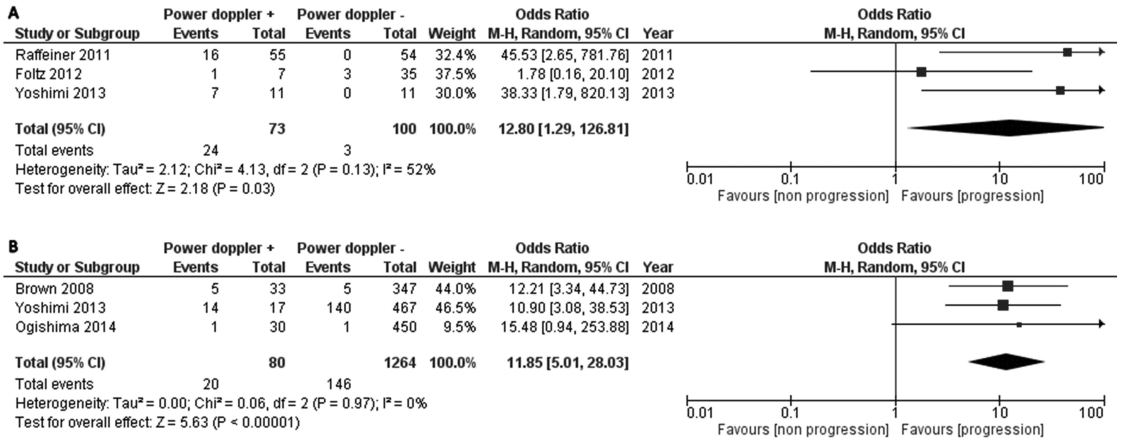


Figure 3. Summary of the association between ultrasonic power Doppler score and risk of progressive bone erosion. A. Patient level. B. Joint level.

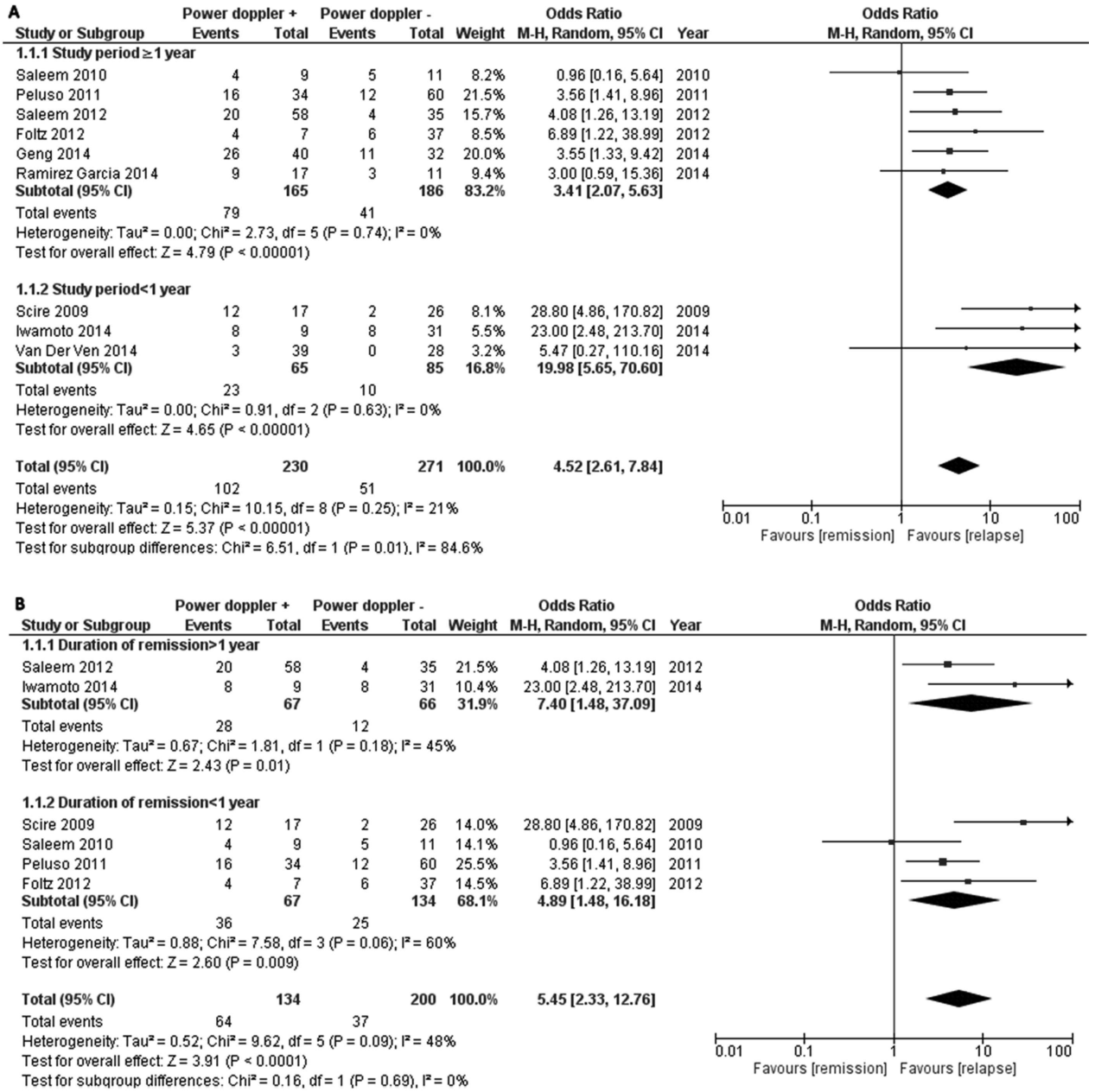
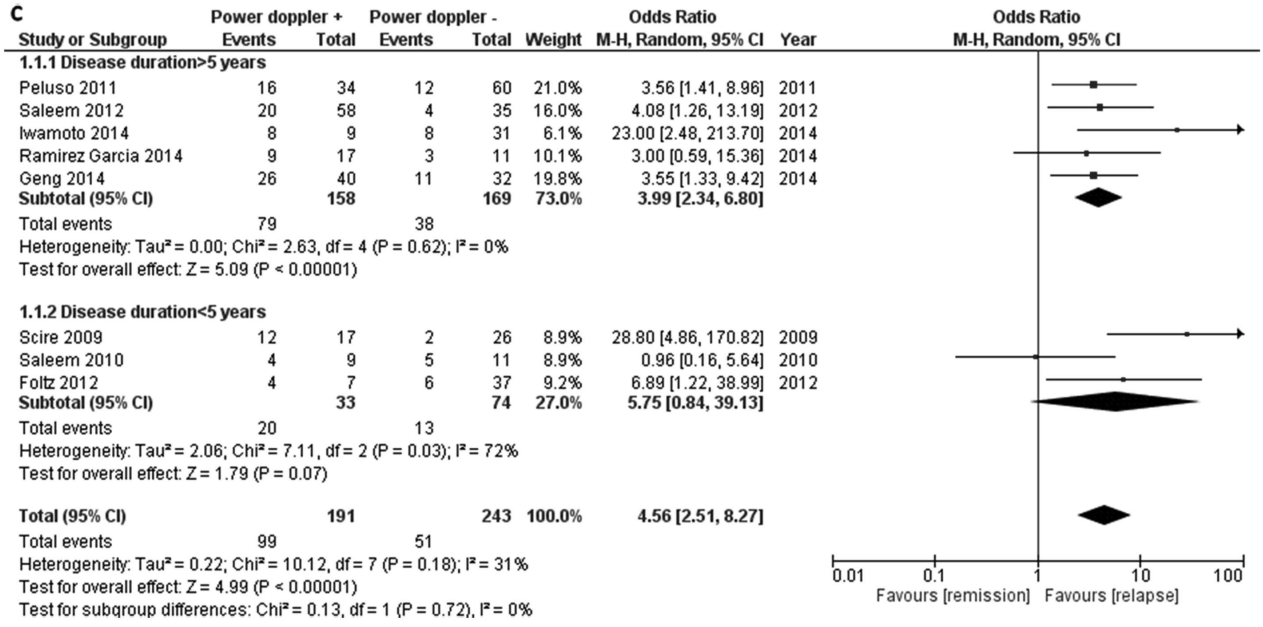


Figure 4A-B. Subgroup analysis of the association between ultrasonic power Doppler score and risk of flare. A. Subgroup of study period (cutoff point of 1 yr). B. Subgroup of duration of remission (cutoff point of 1 yr).

$p < 0.01$)[21]. In other words, US PD positivity is obviously related to histopathological activity in patients with RA who are in superficial clinical remission, which might give a reasonable explanation of the susceptibility to flare. At the same time we also found the risk of flare in patients with GS positivity was 3.69 times as high as that in patients negative for GS. Although it might imply a possible predictive value of GS positivity, the interaction between GS and PD could not be neglected. With little identification between fibrous tissues and active synovitis, GS signals only reflected the presence of synovium tissues[22]. Thus the predictive value of GS independent of PD is still unknown.

In bone erosion, the risk of progression in patients with PD positivity was 11.85 and 12.80 times as high as that in patients with PD negativity on joint level and patient level, respectively. In addition, the range of CI of OR in joint level was much smaller than that in patient level. This phenomenon could be explained by the effect of synovial inflammation on each joint. A previous study confirmed that the cause of bone destruction was sustained synovial inflammation[23]. Because active synovitis in 1 joint, reflected by PD positivity, led to structural progression in that joint, it was much easier to



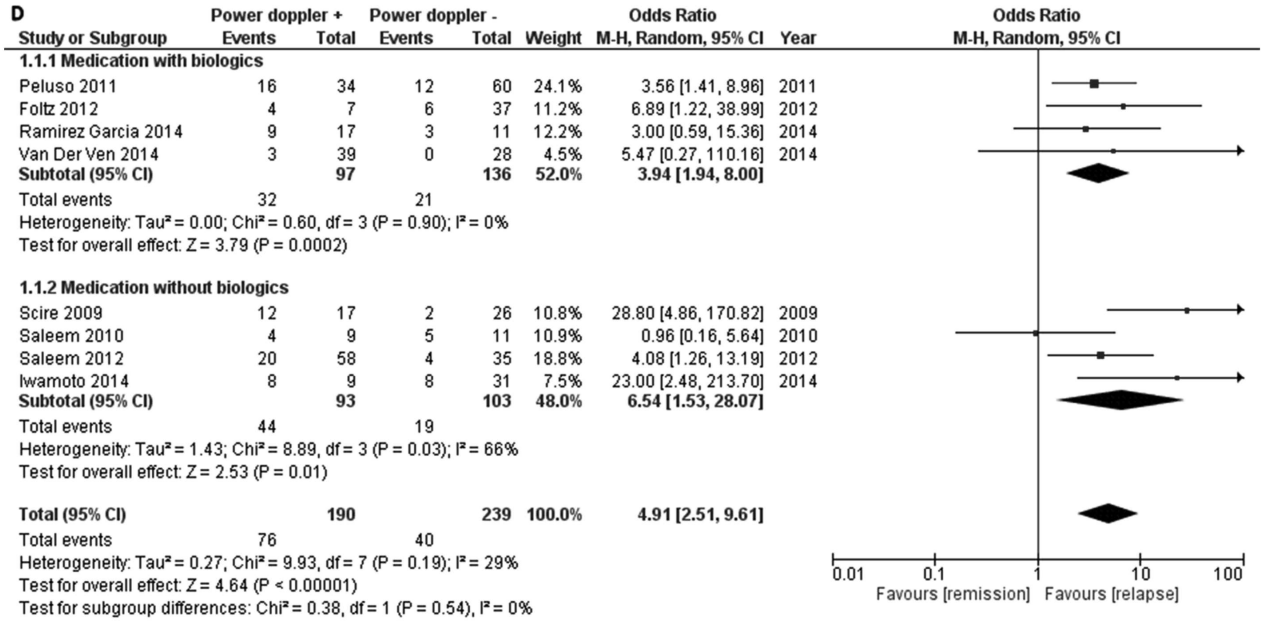


Figure 4C-D. C. Subgroup of disease duration (cutoff point of 5 yrs). D. Subgroup of medication.

understand the higher accuracy of PD positivity in predicting progression on joint level.

Negative results were obtained from the subgroup analyses of disease duration, duration of remission, and medications, indicating no predictive values of these variables for risk of flare. Nevertheless, in the subgroup analysis of shorter study period, a higher risk of flare was observed. After reviewing all the 3 articles that documented the time to relapse, we discovered that an average time to relapse was within 1 year[7,8]. The probability of relapse remains high within a certain period of time, and there might be a predisposition to flare in a certain group of patients with RA. Studies focused on the pathogenesis of flare were extremely rare. Some researchers showed that the alteration of popliteal lymph node volume was associated with arthritic flare in mice. The lymph node expanded and subsequently collapsed before and during the flare, accompanied by the migration of a subset of B cells[24,25]. But this is apparently not enough to clarify the reason for early flare in RA.

Further, musculoskeletal US, the evaluation tool, should also be taken into account. Power Doppler score at remission might have a predictive value for flare only in the short term.

A few studies had begun to address the significance of cumulative PD scores during the study period[26,27]; however, they mainly focused on the value of cumulative PD scores in the field of structural progression, not the arthritic flare.

Through our cumulative metaanalysis, we reaffirmed the predictive value and the predictive accuracy of US PD positivity on risk of flare in patients with RA who are in clinical remission. RA patients with subclinical synovitis may require a cautious adjustment in medications and frequent surveillance during followup. Hence, achieving US remission and implementing an US-guided treatment strategy are becoming inevitable trends in the management of RA.

Our study had some limitations. First, the accuracy of our study was affected by the exclusion of an eligible abstract with key data inaccessibility. Second, no significant effect was observed in the subgroup analysis of duration of remission, which was in contrast to our clinical experience. However, Tokai, *et al*[28] once showed that a longer duration of remission went along with a lower PD score, probably meaning a lower risk of future relapse. We suspected the reason for our negative results was the lack of attention and subsequent sketchy records of this variable in the selected articles. As a result, deeper analysis on the effect of duration of remission still needs to be performed in future studies.

US PD positivity has a predictive value for flare and progressive bone erosion in patients with RA who are in clinical remission. The predictive ability is not influenced by duration of remission, disease duration, or medications. In addition, patients tend to experience an early relapse, mainly within 1 year, for unknown reasons. Therefore, further studies are needed to better understand the pathogenesis of RA flare, to bring about improved prognosis for patients with RA.

ACKNOWLEDGMENT

The authors thank Guangtao Li and Yuansheng Huang for their help with the statistical analysis.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

REFERENCES

1. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631-7.
2. Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M, Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004;50:36-42.
3. Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;58:2958-67.
4. Zufferey P, Moller B, Brulhart L, Tamborrini G, Scherer A, Finckh A, et al. Persistence of ultrasound synovitis in patients with rheumatoid arthritis fulfilling the DAS28 and/or the new ACR/EULAR RA remission definitions: results of an observational cohort study. Joint Bone Spine 2014;81:426-32.
5. Brown AK, Quinn MA, Karim Z, Conaghan PG, Peterfy CG, Hensor E, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. Arthritis Rheum 2006; 54:3761-73.
6. Geng Y, Han J, Deng X, Zhang Z. Presence of power Doppler synovitis in rheumatoid arthritis patients with synthetic and/or biological disease-modifying anti-rheumatic drug-induced clinical remission: experience from a Chinese cohort. Clin Rheumatol 2014;33:1061-6.
7. Saleem B, Brown AK, Quinn M, Karim Z, Hensor EM, Conaghan P, et al. Can flare be predicted in DMARD treated RA patients in remission, and is it important? A cohort study. Ann Rheum Dis 2012;71:1316-21.
8. Iwamoto T, Ikeda K, Hosokawa J, Yamagata M, Tanaka S, Norimoto A, et al. Prediction of relapse after discontinuation of biologic agents by ultrasonographic assessment in patients with rheumatoid arthritis in clinical remission: high predictive values of total gray-scale and power Doppler scores that represent residual synovial inflammation before discontinuation. Arthritis Care Res 2014;66:1576-81.
9. Foltz V, Gandjbakhch F, Etchepare F, Rosenberg C, Tanguy ML, Rozenberg S, et al. Power Doppler ultrasound, but not low-field magnetic resonance imaging, predicts relapse and radiographic disease progression in rheumatoid arthritis patients with low levels of disease activity. Arthritis Rheum 2012;64:67-76.
10. Yoshimi R, Hama M, Takase K, Ihata A, Kishimoto D, Terauchi K, et al. Ultrasonography is a potent tool for the prediction of progressive joint destruction during clinical remission of rheumatoid arthritis. Mod Rheumatol 2013;23:456-65.
11. Nguyen H, Ruyssen-Witrand A, Gandjbakhch F, Constantin A, Foltz V, Cantagrel A. 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. Rheumatology 2014;53:2110-8.
12. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427-37.
13. Scire CA, Montecucco C, Codullo V, Epis O, Todoerti M, Caporali R. Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse. Rheumatology 2009;48:1092-7.
14. Saleem B, Keen H, Goeb V, Parmar R, Nizam S, Hensor EM, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? Ann Rheum Dis 2010;69:1636-42.
15. Peluso G, Michelutti A, Bosello S, Gremese E, Tolusso B, Ferraccioli G. Clinical and ultrasonographic remission determines different chances of relapse in early and long standing rheumatoid arthritis. Ann Rheum Dis 2011;70:172-5.
16. Ogishima H, Tsuboi H, Umeda N, Horikoshi M, Kondo Y, Sugihara M, et al. Analysis of subclinical synovitis detected by ultrasonography and low-field magnetic resonance imaging in patients with rheumatoid arthritis. Mod Rheumatol 2014;24:60-8.
17. Ramirez Garcia J, Ruiz-Esquide V, Celis R, Cuervo A, Cabrera S, Inciarte-Mundo J, et al. Sonographic and clinical characterization of a prospective cohort of patients with rheumatoid arthritis in clinical remission. Preliminary results [abstract]. Ann Rheum Dis 2014;73 Suppl 2:888.
18. Van Der Ven M, Kuijper M, Gerards A, Tchetverikov I, Weel A, Van Zeben J, et al. Can we use ultrasound to identify rheumatoid arthritis patients in remission who can taper their medication [abstract]? Ann Rheum Dis 2014;73 Suppl 2:107.
19. Raffeiner B. Usefulness of power Doppler to predict radiological

damage in RA patients in clinical remission by TNF blockers [abstract]. Ann Rheum Dis 2011;70 Suppl 3:76.
20. Szekanecz Z, Pakozdi A, Szentpetery A, Besenyei T, Koch AE. Chemokines and angiogenesis in rheumatoid arthritis. Front Biosci (Elite Ed) 2009;1:44-51.
21. Takase K, Ohno S, Takeno M, Hama M, Kirino Y, Ihata A, et al. Simultaneous evaluation of long-lasting knee synovitis in patients undergoing arthroplasty by power Doppler ultrasonography and contrast-enhanced MRI in comparison with histopathology. Clin Exp Rheumatol 2012;30:85-92.
22. Taylor PC, Steuer A, Gruber J, Cosgrove DO, Blomley MJ, Marsters PA, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. Arthritis Rheum 2004;50:1107-16.
23. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
24. Li J, Kuzin I, Moshkani S, Proulx ST, Xing L, Skrombolas D, et al. Expanded CD23(+)/CD21(hi) B cells in inflamed lymph nodes are associated with the onset of inflammatory-erosive arthritis in TNF-transgenic mice and are targets of anti-CD20 therapy. J Immunol 2010;184:6142-50.
25. Bouta EM, Li J, Ju Y, Brown EB, Ritchlin CT, Xing L, et al. The role of the lymphatic system in inflammatory-erosive arthritis. Semin Cell Dev Biol 2015;38:90-7.
26. Hama M, Uehara T, Takase K, Ihata A, Ueda A, Takeno M, et al. Power Doppler ultrasonography is useful for assessing disease activity and predicting joint destruction in rheumatoid arthritis patients receiving tocilizumab—preliminary data. Rheumatol Int 2012;32:1327-33.
27. Ikeda K, Nakagomi D, Sanayama Y, Yamagata M, Okubo A, Iwamoto T, et al. Correlation of radiographic progression with the cumulative activity of synovitis estimated by power Doppler ultrasound in rheumatoid arthritis: difference between patients treated with methotrexate and those treated with biological agents. J Rheumatol 2013;40:1967-76.
28. Tokai N, Ogasawara M, Gorai M, Matsuki Y, Yamada Y, Murayama G, et al. Predictive value of bone destruction and duration of clinical remission for subclinical synovitis in rheumatoid arthritis patients. Mod Rheumatol 2015;25:540-5.